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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

WILLIAM DOCK

KATHLEEN E. ROBERTS, JEROME J. DECOSSE and HENRY T. RANDALL

HON. BERNARD BOTEIN

GREGORY ZILBOORG

PARKINSON'S DISEASE: MEDICAL AND SURGICAL MANAGEMENT

Transcription of a Panel Meeting on Therapeutics

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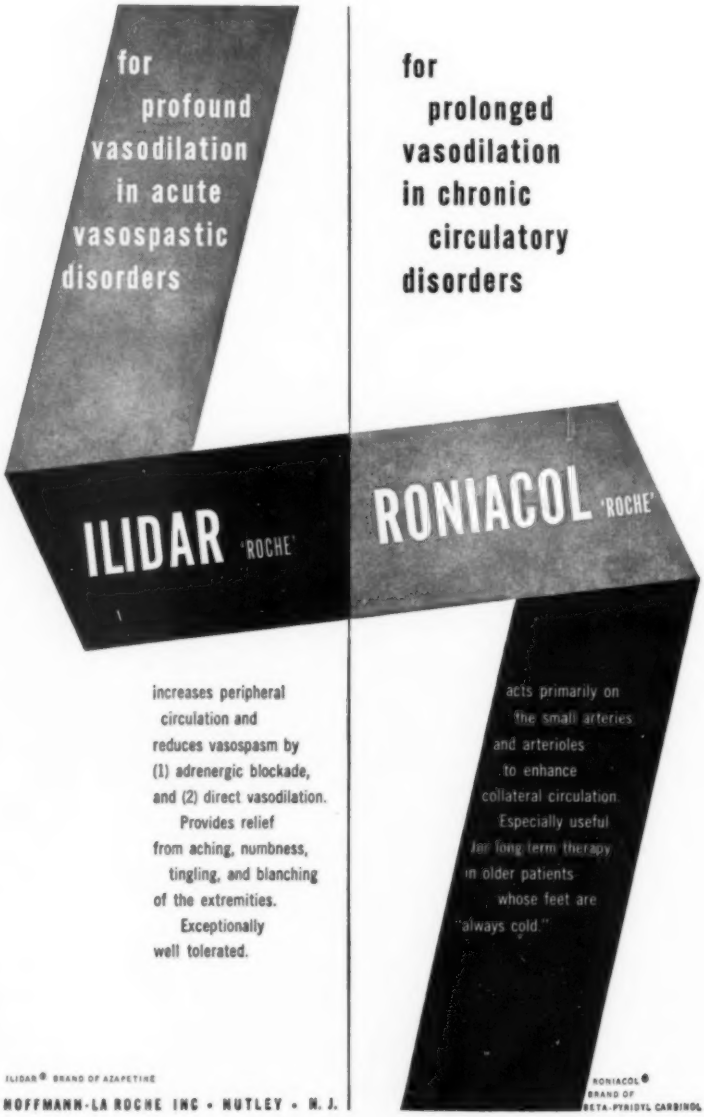
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2. Roskam, J., VanCawenberge, H.: Abst. in J.A.M.A., 151:248 (1953).
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4. Holt, K.S., et al.: Lancet, 2:1144 (1954).
5. Spies, T.D., et al.: J.A.M.A., 159:645 (Oct. 15, 1955).

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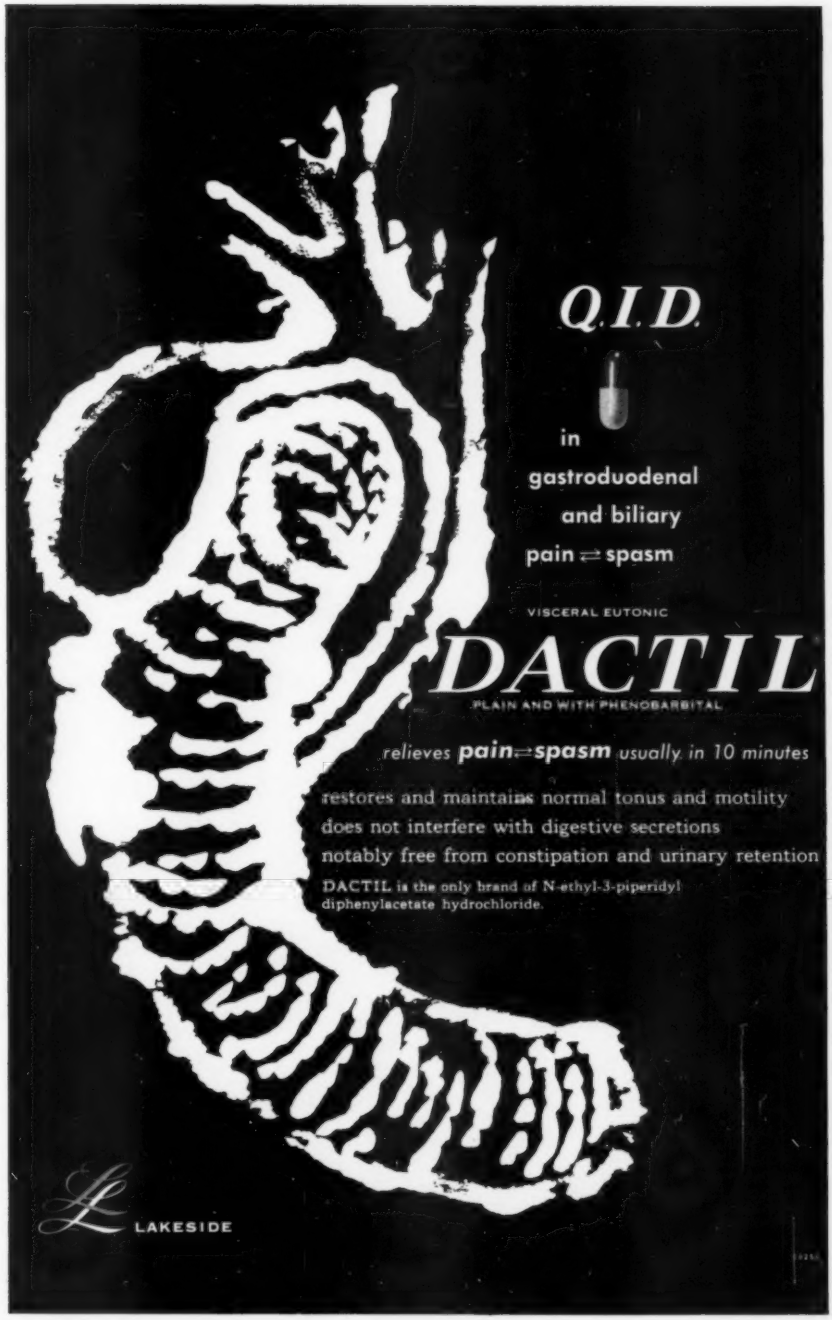
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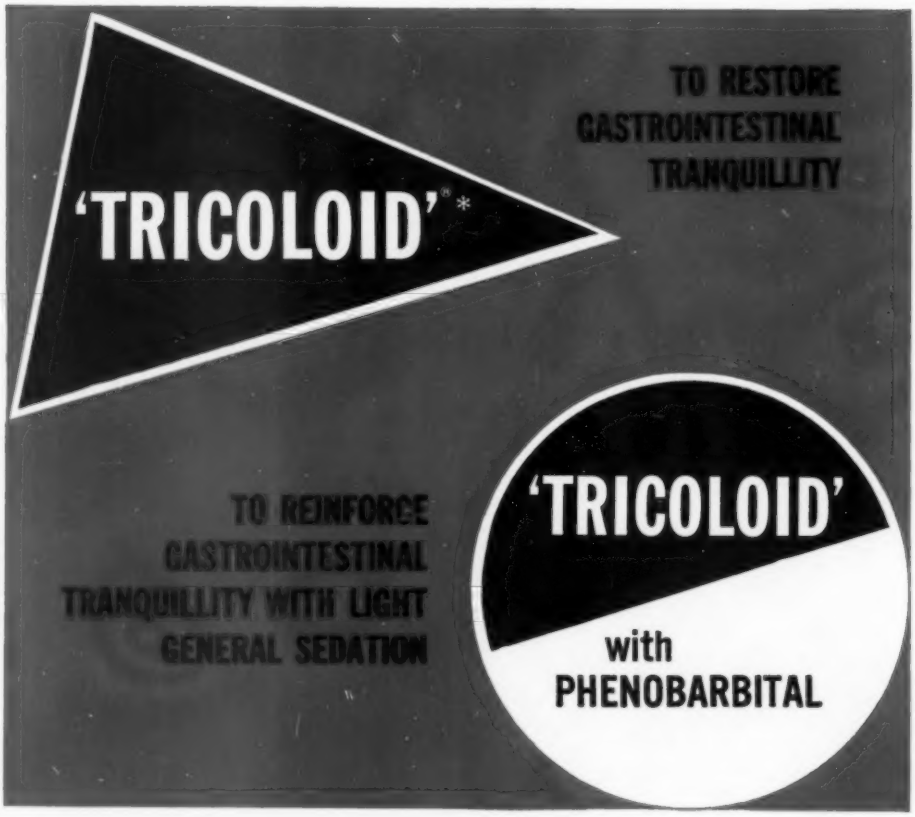

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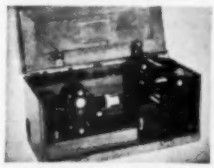

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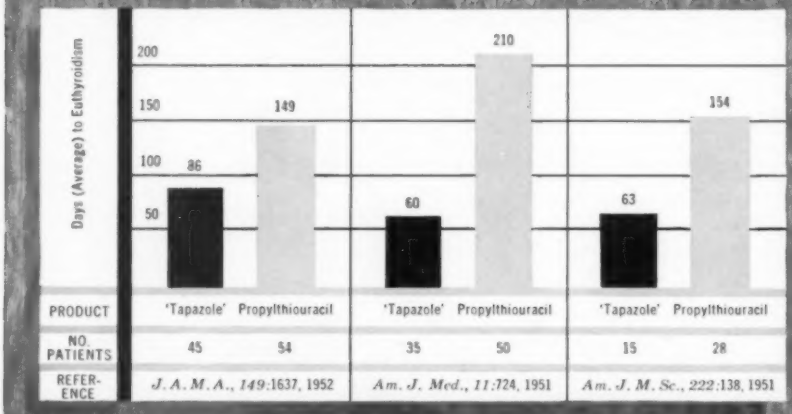

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 32, NO. 3 MARCH 1956

AGING OF THE MYOCARDIUM*

WILLIAM DOCK

Professor of Medicine, State University of New York College of Medicine at New York City, Brooklyn

THERE are so many examples of a contrast between apparent age and the conservation or loss of function that we should not be surprised that this contrast is great in the myocardium. A bald or white-haired man, with wrinkled face and store-bought teeth, may turn out to be a superlative chess-player or contributor to scientific progress, and the wizened, dark-brown heart of a 90 year old man may have beaten regularly and maintained an adequate circulation as he died of cancer. On the other hand, a good-looking young man may turn out to be the superannuated baseball hero of the previous decade, no longer able to hit or run, and the fine, large, pink heart may be that of a woman 55 years old, who died of congestive heart failure and auricular fibrillation, with no valvular disease or hypertension.

With aging, all hearts accumulate pigment granules, which are concentrated close to the nuclei. If the heart muscle remains efficient, and therefore can atrophy as the demands of basal metabolic load, digestion and physical activity decline with advancing years, the ratio of pigment to myoglobin and myofibrils is high and we see a small

* Presented at the 28th Graduate Fortnight on *Problems of Aging*, of The New York Academy of Medicine, October 11, 1955.

brown heart. On the other hand, if the myocardium becomes inefficient, if more muscle mass is needed for each unit of work, or if the load imposed by valvular disease, hypertension, or high volume flow of blood leads to hypertrophy, then the ratio of pigment to myoglobin and myofibrils is low. Microscopically as well as grossly, the inefficient or overloaded heart looks more normal in the aged, than the efficient muscle carrying its small load.

In addition to changes in the pigment content, and the diffuse atrophy of senile inanition, the hearts of obese sedentary Americans often show, even before 50, striking local atrophy and even complete disappearance of myocardial fibers in the right ventricle and right atrium. In these hearts, yellow adipose tissue, continuous with the abundant epicardial fat, or developing *de novo* under the endocardium, completely replaces myocardial tissue. In extreme examples, much of the right atrium near the annulus looks like pure fat when sectioned.

There is no doubt whatever that the aging heart can beat efficiently in most people as long as the coronary system is not damaged by a disease which in itself is not a part of the aging process. Even chronic valvular disease and hypertension, or the high flow imposed by parkinsonism or by Paget's disease, may fail to produce a dilated and failing heart in a man of 70 or more. But statistics, rather than the outstanding exception, must be used in approaching such a problem, and the figures show clearly that with any type of injury or embarrassment to the heart, dilatation and failure occur far more frequently after 50 than before 30 years of age. Army personnel dying of coronary disease before 40 had little heart failure, and no right ventricular failure at all. Those dying of coronary disease after 55 years of age exhibited left heart failure in over 50 per cent, right heart failure in nearly 20 per cent of cases. Heart failure and auricular fibrillation are frequent even in mild hyperthyroidism after 50; they are unknown, even in severe Graves' disease, before 30. Severe hypertension rarely causes heart failure in young people; mild hypertension often is the only demonstrable circulatory embarrassment in elderly cardiac invalids. Nor is it merely the tendency to auricular fibrillation and congestive failure which distinguishes old hearts from young ones. Young people with complete heart block rarely have the syncopal attacks, due to ventricular stand-still, which so often occur in elderly people with heart block. The old heart has neither as dependable a set of stand-by pacemakers,

as dependable machinery for conducting the normal impulse and suppressing ectopic foci, nor as efficient a mechanism for converting chemical to contractile energy, as did the same heart a few decades earlier in life.

It is not known what differences actually exist between young and old hearts in the various factors which could alter the irritability and efficiency of the muscle, but perhaps it is worth while to state what some of these factors could be. The work of Szent-Györgyi and of Salter showed that normal plasma contains a steroid which increases myocardial efficiency, but the level of this substance in the plasma of young and old, and the responsiveness of young and old hearts to given levels of the steroid are unknown. The ionic balance of sodium, magnesium, calcium, and potassium in the fluid about the myofibrils is known to alter myocardial efficiency; the effect of age on this balance is unknown. The proteins of the myofibrils, actin and myosin, and the adenosine phosphates of muscle react with each other to cause contraction and relaxation, but the effects of aging on these reactions are unknown. Finally, the mechanism by which lactate, pyruvate, dextrose or fat are burned and provide energy to the contractile system may be altered by age, but no data on this have been obtained. Any or all of these may be affected by the aging process, and the change might involve either the amount of energy available for a contraction after a long rest interval, or merely the rate at which capacity for maximal contractile efficiency was restored after each beat.

The clinical impression is that the greatest change caused by aging of the myocardium is delay in recovery of contractility and irritability. It is known that most arrhythmias are due to delay in recovery of irritability, with prolongation of both relative refractory and supranormal phases of irritability facilitating the origin of ectopic beats or rhythms. The older hearts are much more prone to these disorders. In young people, ventricular rates over 200 per minute may last for many hours or even days before the heart dilates and signs of heart failure set in. In people over 60, heart failure is rare with complete heart block or in the fevers with bradycardia, such as typhoid. But rates of 120 to 150, due to paroxysmal tachycardia or to fever, frequently precipitate failure in older people. It would therefore appear that the old myocardium has a slow rate of recovery, but contracts well as long as there is an adequate period for rest between beats. This is why simple

emotional tachycardia, with no rise in blood pressure, so often seems to be a factor in precipitating acute heart failure in people over 50.

Ever since heart failure was precipitated by overdosage of desoxycorticosterone, in treating Addison's disease, it has been realized that excessive sodium ingestion or retention led to heart failure not only by hastening edema formation, but by actually impairing myocardial efficiency. Much experimental and clinical evidence has confirmed an idea that goes back to the observations of Ringer on the effect of electrolytes on the heart beat. There is an ideal balance of metallic ions, at which the myocardium functions best, and its efficiency is impaired when this balance is altered. Deficits of potassium and excesses of sodium seem to be particularly bad for the heart. The former is frequent with severe illness, and in the diabetic; the latter is the normal state of civilized man, with a daily sodium to caloric intake from 10 to 30 times that of his anthropoid cousins and 5 to 10 times that of primitive races or the sweating masses of poor people throughout most of the world today. Thus, it is difficult to be sure that the loss of myocardial efficiency with age is actually due to an involutional process, and not the cumulative result of decades of injury due to excessive salt intake and a sedentary existence, with low salt need. Perhaps the best evidence for the view that aging alone can impair myocardial function is that auricular fibrillation and heart failure occur in old horses, which have not been on high salt diets and have faultless coronary arteries.

It should be emphasized that none of these anatomical or chemical changes impair the ability of the myocardium to respond to modest loads of work; none of them actually cause heart failure. All of them reduce the ability of the heart to meet sudden increases in rate or in work per beat, and thus they predispose the heart to fail during febrile illnesses, after operations or pulmonary embolism, or with the chronic causes of cardiac strain—Parkinson's disease, Paget's disease, leukemia, anemia, and hyperthyroidism—which so often occur in elderly people and raise the pulse rate and the stroke volume of the heart. Pulmonic or systemic hypertension, also common in aging Americans, brings to light the inability of old hearts to cope with a heavy burden.

Whatever the background of failure of the myocardium, this type of disorder responds very well to digitalis and to salt restriction. Unfortunately, elderly people are often "set in their ways" and do not take kindly to diets of rice, green vegetables, salt-free cheese and

boiled meat. As Kempner and others have shown, the cardiacs who do adhere to such diets, with sodium contents comparable with those in the natural diets of the great apes, show striking benefit even without digitalis. But most of our patients prefer a less physiologic therapeutic program, based on mercurial diuretics, digitalis and Diamox. It is unfortunately true that just as no synthetic institutional program can ever substitute for a large and affectionate family in providing the proper environment for an aging man or woman, no program of drugs ever will provide a satisfactory replacement for a physiologic regime of activity and diet, in an atmosphere of pure air. The elderly cardiac probably fared better at Cos or Epidauros, in the hands of Hippocrates and his disciples, than he does in the smoke-filled waiting rooms of our doctors' offices and with the powerful therapeutic agents available today.

The most encouraging thing about myocardial aging is that the rate of progress often is slow in those who develop symptoms because of intercurrent illness such as myocardial infarction, if a sound program of digitalization and sodium restriction or depletion is adhered to. We have seen patients with excellent capacity for physical effort ten, and in two cases, twenty years after their initial bouts of acute pulmonary edema. This can only happen when the physician and the patient refuse to accept the idea that aging of the heart (presbycardia) or what has been called arteriosclerotic heart disease, is a relentlessly progressive disorder which of itself is fatal.

As with what is called cerebral arteriosclerosis, the aging changes in the heart can be imitated by vitamin deficiency and endocrine imbalance. Until all these possible causes or potentiators of dysfunction have been treated or completely excluded, it is improper to put the blame on involutional change. Just as a mind which might continue to function adequately in a calm home, with old friends and affectionate relatives, will seem to disintegrate in a hospital, a nursing home, or a psychiatric ward, so a heart which would give no trouble on a good diet and in a tranquil person rapidly fails during periods of social or family stress, with diets high in sodium and low in water-soluble vitamins. Aging of the heart or mind do least damage and progress very slowly when the individual lives under optimal conditions, and the manifestations seen under other situations can be corrected and further symptoms prevented when the patient receives and accepts sound and optimistic advice.

FLUID AND ELECTROLYTE PROBLEMS IN THE SURGERY OF THE AGED*

KATHLEEN E. ROBERTS, JEROME J. DECOSSE
and HENRY T. RANDALL

It is generally recognized that plasma electrolytes and the physiological regulation of electrolyte balance in the geriatric patient do not differ qualitatively from that of the younger patient. Quantitatively, however, the margin of safety and the ability to compensate under stress may be impaired in the aged.[1-4] An understanding of the common difficulties which may be anticipated in surgery of the aged patient is therefore important for successful management. In our experience, three major alterations should be given special consideration, since they are those which we have encountered most frequently in the pre- and postoperative intervals in aged patients.

The alterations which are common and the periods in which they are seen include: 1) in the preoperative period, contraction of blood volume and electrolyte alterations resulting from operative preparation; 2) in the postoperative period, the electrolyte changes which arise from the normal response to surgery; 3) abnormalities which result from pulmonary dysfunction following surgery. The purpose of this paper is: 1) to present the common alterations which may occur in the pre- and postoperative intervals; and 2) to propose that surgery need not be denied or compromised in the elderly patient.

PREOPERATIVE INTERVAL

Because of the greater incidence of pulmonary, cardiac, metabolic and renal disease in the aged, the initial workup must be more complete than in the young patient. The recognition of metabolic disturbances and reflected plasma chemical abnormalities have been

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We are indebted to Dr. H. N. Bane and Dr. J. W. Poppell for the privilege of incorporating their unpublished data in this paper.

TABLE I—ELECTROLYTE CONCENTRATION IN AN ISOLATED ILEAL SEGMENT FOLLOWING THE INTRODUCTION OF ISOTONIC MAGNESIUM SULPHATE SOLUTION

Time Min.	*Intestinal Contents*			*Plasma*		
	Sodium	*Potassium mEq/L*	*Chloride*	*Sodium*	*Potassium mEq/L*	*Chloride*
0	40 cc. of Isotonic $MgSO_4$					
120	132	2.17	68.7	147	4.9	117

elaborated elsewhere and therapy outlined for correction.[5-9]

A special problem facing the physician is one resulting from surgical preparation. It has recently become evident that patients who are undergoing standard bowel preparation for gastrointestinal surgery frequently display a hyperchloremic acidosis and negative potassium balance following the period of preparation with purgatives.[10] The mechanisms of these changes are illustrated in Tables I and II. Basically, it has been shown that a poorly absorbed solution such as magnesium sulphate, when introduced into the intestinal lumen, will result in a secretion of electrolytes into the lumen. The concentration of electrolytes will vary for each intestinal segment and if the solution is hypertonic to the plasma, water will also shift into the lumen of the bowel.[11, 12] This is illustrated in Table I, which shows the data from an experiment carried out by Bane.[11] In this experiment isotonic magnesium sulphate was placed in an isolated ileal segment of a dog and the shift of sodium, chloride and potassium measured over a two hour interval. As shown, the net shift of electrolytes resulted in a concentration of 132 mEq. of sodium, 68.7 mEq. of chloride and 2.17 mEq. of potassium per liter. Although it was apparent in these studies that concurrent electrolyte shifts were occurring both from the lumen to the plasma and from the plasma to the lumen of the bowel, the net shifts of sodium, chloride and potassium were always quantitatively greater from plasma to lumen when a poorly absorbable solution was introduced. In the jejunum, electrolyte shifts also occur, but differ as regards composition. Whereas sodium and chloride are secreted in about equimolar concentration in the jejunum and upper ileum, the concentration of chloride in lower bowel segments is less than the

TABLE II—PLASMA ELECTROLYTES IN A PATIENT BEFORE AND AT THE COMPLETION OF A FIVE DAY BOWEL PREPARATION

	Sodium	*Potassium*	*Plasma Carbon Dioxide mEq/L*	*Chloride*	*pH*
Before bowel preparation	142	4.9	28	102	7.43
After bowel preparation	140	5.3	24.2	116	7.33

concentration of sodium. This is also illustrated in Table I, which shows that approximately half of the sodium and potassium may be shifted into the lumen with chloride and presumably a major fraction of cation is secreted with bicarbonate. It is noteworthy that the bicarbonate concentration of lower bowel content is higher than that found in the plasma, whereas chloride concentration of the lower ileum and large bowel is less than that normally found in the plasma.[9] These concentrations are not unlike those which have been described in diarrhea contents or ileostomy drainage.[6] Logically, it would be expected that such external losses of sodium and potassium in excess of chloride, if excessive and unreplaced, would result in a plasma hyperchloremia and acidosis. In the patients studied by us such was found to be the end result of vigorous bowel purgation. This is illustrated in a patient shown in Table II, whose plasma electrolytes and pH were essentially normal prior to a five day bowel preparation. At the end of the preparatory interval the patient displayed a plasma hyperchloremia and acidosis. Similar plasma findings have been demonstrated in eight of nine patients studied by us before and at the completion of bowel preparation for surgery.[10] Cognizance of the potential existence and hazards of hyperchloremic acidosis preoperatively, compels its treatment which consists essentially of rehydration and alkali administration as bicarbonate or lactate. Usually this is satisfactorily accomplished the day prior to surgery, by oral or intravenous administration of 100-200 mEq. of sodium bicarbonate or lactate. A major consideration arising from these observations is that the patient should not be denied adequate bowel preparation, but rather, that the electrolyte derangements should be recognized and treated preoperatively.

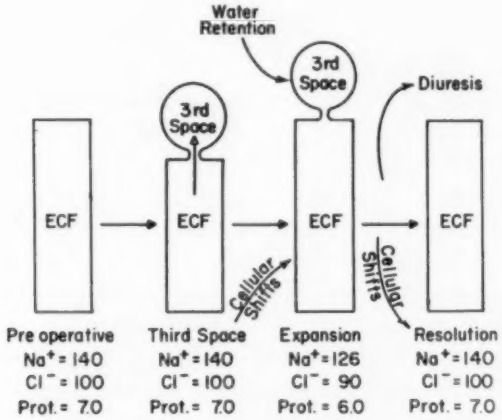

Figure 1—Diagrammatic representation of the postoperative third space and plasma electrolyte changes.

Preoperative Blood Volume

It is not uncommon to find a contracted blood volume preoperatively in the aged patient.[2, 13] In the majority of patients the contracted volume has been related to one of four factors: 1) gastrointestinal bleeding; 2) inadquate dietary intake; 3) chronic renal disease; or 4) malignancy. Since the contracted blood volume may not be revealed by any alteration in the hematocrit, it may easily escape detection. For this reason preoperative blood volumes in the aged patient are essential. Since the patient is usually "adjusted" to his contracted volume and sudden expansion has been known to result in congestive failure, daily replacement of 250 cc. of blood until correction is achieved affords a conservative and successful approach to this problem.

Postoperative Interval

The postoperative response to surgery is not significantly different from the response which has been described in younger members of the populace. Fundamental to therapy in the postoperative period is an understanding of the normal shifts of water and electrolytes which occur following major surgical procedures.[6, 10, 14, 15] Essentially, these

may be outlined as follows: In the immediate three to four days following surgery there is the formation of a "third space," and an associated extracellular expansion of water. This is illustrated in Figure 1. As shown, there is an initial shift of water and extracellular electrolytes to the third space, which may be into the pleural cavity, bowel, peritoneal cavity, pelvis or extremities. Retention of exogenously administered water and sodium is also commonly observed in the first few days postoperatively. The resultant retention of water and compensatory shifts of water from the intracellular to the extracellular compartment, result in dilution of the major extracellular components. The net result will be: 1) an expanded extracellular fluid; 2) hyponatremia and hypochloremia secondary to dilution* (Fig. 1); 3) a drop in hematocrit and protein which is also secondary to the hydremia. During the interval of these changes, urine volume may be low with a high specific gravity. During the resolution of the third space diuresis ensues, the excretion of sodium increases and losses of water and sodium may exceed intake. At the completion of resolution the return of plasma composition and the hematocrit to normal is the usual finding.

While these changes which have been observed postoperatively are not peculiar to the aged patient, certain features in this group of patients are noteworthy. 1) In the patient, with pre-existent cardiac dysfunction and a previously restricted sodium intake, the drop in plasma and sodium during the third space period may be more marked. 2) The administration of sodium must be carefully considered. 3) The expansion of the extracellular fluid may compromise circulatory dynamics as the result of pre-existent myocardial damage. Hence it is important to guard against overloading the circulation by unnecessary transfusions or excessive saline administration.

Hormonal Response: The adrenal response to surgery and the role of the adrenal hormones in the acute postoperative period has been recognized and it has been established that the "alarm reaction" following surgery is a major sequence.[15] Release of anti-diuretic-hormone has been indicted in the antidiuretic response during the period of acute water retention.[16] However, the importance of this factor and its mechanism of release in the postoperative extracellular dilution remains obscure.

* Total extracellular sodium (as calculated from the plasma sodium concentration and extracellular sucrose space) may actually be greater in this postoperative interval.

TABLE III—MAJOR DIAGNOSTIC FINDINGS IN RENAL SHUTDOWN AND POSTOPERATIVE DEHYDRATION

	Sodium	*Plasma Potassium mEq/L*	*Chloride*	*Blood Urea mgm%*	*Hematocrit %*	*Urine Spec. Grav.*	*Urine Vol.*
Dehydration (plus third space effect)	±	↑	±	↑	+ −	↑↑	↓
Renal Shutdown (plus third space effect)	↓	↑↑	↓	↑↑	↓	↓	↓↓

DEHYDRATION AND RENAL SHUTDOWN DURING THE POSTOPERATIVE PERIOD

The differential diagnosis between renal shutdown and dehydration is a common problem facing the clinician in evaluating early postoperative oliguria in the elderly patient who has had conservative fluid and electrolyte replacement and questionable renal function. This is particularly true in patients who have had a transfusion reaction, shock or severe trauma. Since the "third space effect" and oliguria will be superimposed on either of these situations the changes which occur are additive. Factors which may aid in establishing the correct diagnosis are listed in Table III. The specific gravity of the urine is of the utmost importance; if the specific gravity is low renal shutdown assumes more prominence, whereas an elevation of specific gravity may indicate dehydration. In renal shutdown the hematocrit and protein may drop while dehydration is accompanied by a stable or rising hematocrit. Plasma sodium and chloride concentrations remain unchanged or elevated if the patient is dehydrated and concentration decreases if renal shutdown exists. In renal shutdown the blood urea nitrogen and potassium rise precipitously, whereas dehydration causes only minor elevations of these plasma constituents. It is particularly important to differentiate between renal shutdown and dehydration, since excessive fluid therapy may be hazardous if marginal pulmonary or cardiac reserve exists in the patient.

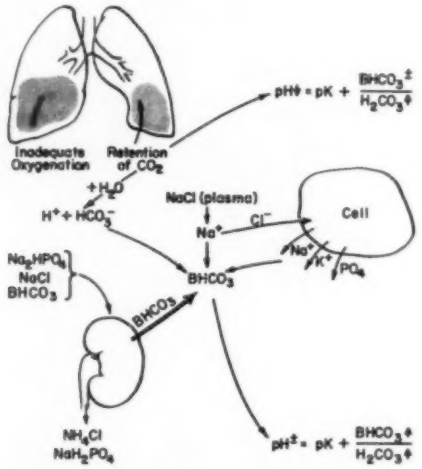

Figure 2—Physiological compensations in respiratory acidosis (see text).

Respiratory Acidosis

The higher incidence of pulmonary disease and postoperative atelectasis is generally recognized in the older age group.[1-3] Therefore rigorous attention to adequate ventilation and the recognition of pulmonary acidosis and accompanying hypoxia are important. The physiological compensations occurring in respiratory acidosis have been well described and are diagrammed in Figure 2.[17-20] They include: 1) an initial retention of carbon dioxide with elevation of carbonic acid and a drop in plasma pH; 2) a shift of chloride to the intracellular compartment, leaving behind an equal moiety of sodium in the extracellular fluid; 3) extracellular shifts of potassium and sodium; 4) increased renal tubular reabsorption of filtered bicarbonate; and 5) enhanced renal excretion of chloride and phosphate with ammonium and hydrogen ion with a consequent increase in the renal formation of sodium bicarbonate by virtue of ion exchange. As a result of these compensations the total CO_2 content of the plasma rises, chloride concentration falls, and there is little change in sodium and potassium concentration.* If compensations are complete, as is often the case, the extracellular pH will be normal or only slightly decreased.

* Potassium concentration will rise only if there is severe renal impairment or superimposed anoxia.

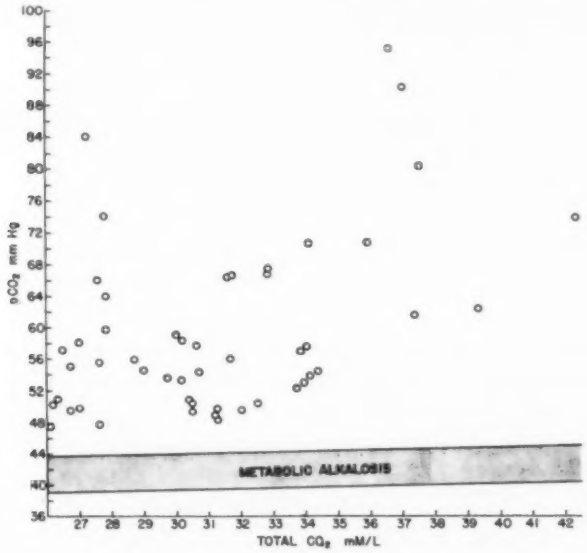

Figure 3—The shaded area represents plasma pCO_2 in patients with metabolic alkalosis who had no deducible evidence of pulmonary disease. The circles represent patients with decreased pulmonary exchange. (Data from J. W. Poppell.)

Respiratory acidosis must be differentiated from metabolic alkalosis, which is not uncommon in the elderly patient who has had an inadequate potassium intake or has been subjected to gastric drainage of chloride.[9] In both respiratory acidosis and metabolic alkalosis total carbon dioxide will be elevated; therefore, the differential diagnosis will evolve itself around the plasma pH, and clinical evidence of cyanosis or inadequate pulmonary ventilation. The finding that pulmonary compensations are minimal in metabolic alkalosis is of fundamental importance[8] in differentiating between metabolic alkalosis and respiratory acidosis. This is illustrated in Figure 3, which summarizes the changes in plasma pCO_2 in the patients with decreased respiratory exchange, who were studied by Poppell.[21] The shaded areas represent the respiratory compensations, as reflected by the plasma pCO_2 in patients without pulmonary disease who had metabolic alkalosis. The plotted points represent the calculated plasma pCO_2 of patients with respiratory disease and as illustrated, the majority of these patients had a plasma pCO_2 greater than the normal of 38-46 mm. Hg. Table IV

TABLE IV—PLASMA FINDINGS IN PATIENTS WITH METABOLIC ALKALOSIS AND RESPIRATORY ACIDOSIS

			Plasma Concentration	
	pCO_2	*pH*	*Total Co_2*	*Chloride*
Metabolic Alkalosis	±	↑	↑	↓
Respiratory Acidosis	↑	± — ↓	↑	↓

summarizes the plasma alterations which may be expected in respiratory acidosis and metabolic alkalosis. In both situations plasma carbon dioxide will be elevated and chloride decreased. In respiratory acidosis, however, the plasma pH will be low or normal and pCO_2 will be greatly increased.

Of major importance is the realization that respiratory acidosis of itself may not be a hazardous clinical entity but that its diagnosis is important because it is often a reflection of anoxia.*[19] The treatment therefore, is not that of correction of the extracellular electrolyte abnormality, but rather energetic efforts to increase ventilation and establish adequate pulmonary exchange of oxygen. The treatment is dependent on the relief of precipitating factors. Ancillary measures include mechanical aids to ventilation, tracheal suction, early ambulation, bronchodilators, antibiotics, expectorants and other agents designed to facilitate removal of secretions.[5] Bronchoscopy or tracheostomy may be life saving during the early postoperative interval. Although a discussion of narcotics is beyond the scope of this paper, the sparing use of these agents is strongly recommended. In the patients seen by us, the efforts to correct postoperative pulmonary difficulties have been discouraging, and mortality of the aged patient with pulmonary disease is greatly in excess of that observed from any other group of electrolyte disturbances we have encountered.

SUMMARY

Three major considerations have been discussed in regard to electrolyte abnormalities in the aged patient undergoing surgery. These include: 1) The occurrence of hyperchloremic acidosis as the result of

* Especially in a patient breathing room air.

preoperative bowel preparation in the elderly patient; 2) normal postoperative alterations in extracellular fluid and electrolytes; and 3) the high incidence of respiratory acidosis and anoxia. It has been stressed that the anoxia which frequently attends respiratory acidosis is common in the elderly patient and is enhanced by postoperative atelectasis. In our experience the morbidity and mortality from pulmonary disease is greater than from any other group of electrolyte disturbances in the postoperative aged patient.

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THE ROLE OF THE PHYSICIAN AS AN EXPERT WITNESS IN CIVIL ACTION*

THE HONORABLE BERNARD BOTEIN

Associate Justice, Appellate Division, New York State Supreme Court

IN 1928 one of our noblest and most urbane men of law spoke in this hall. At that time Judge Cardozo said: "The more I think it over, the more I feel the closeness of the tie that joins our guilds together."

In this spirit of kinship our professions have jointly launched and recently concluded a notable experiment—the Medical Expert Testimony Project. I do not propose to dwell tonight on the splendid results achieved by this project under the leadership of Presiding Justice David W. Peck of the Appellate Division. Not among the least was a demonstration that the two professions can collaborate harmoniously and effectively in coping with a common problem.

The project was born as a result of the acute dissatisfaction that informed members of both professions experienced with the calibre of expert medical testimony in the courts. The quality of such expert testimony simply had to be improved. For example, it was intolerable that one expert would swear that a line on an x-ray picture depicted a fracture of the skull, while another swore it was merely the normal suture line. And the quality has been improved greatly through a magnificent joint effort.

I would like to follow hard on the heels of this project by isolating and holding up for scrutiny a practice that I believe debases the presentation of medical testimony. It is an abuse that has been curbed considerably by the functioning of the medical panels; but I doubt that it can be eliminated effectually without some additional measures. Although I venture to speak only as one individual, I echo the views of a great many persons—judges, lawyers, even doctors, and others—who participate in the court processes.

Since the medical expert testifies mostly in actions for personal injuries arising out of accidents, I shall discuss his role in relation to that type of case only.

* Presented at the Stated Meeting of The New York Academy of Medicine, April 7, 1955, as part of a Symposium "The Doctor in Court." Manuscript received May 1955.

The trial of a lawsuit is essentially a search for the truth. And the physician as an expert witness should play a most important role in aiding and even guiding judge and jury in this search.

Through centuries of experience we men of law have evolved ground rules designed to bring out the facts during a trial as fairly and thoroughly as is possible. And we have also formulated principles of law that are designed to work what the man in the street would regard as justice. These principles of law, however, must be applied to facts—facts as found in the courtroom, which are not necessarily the true facts.

Now, it is difficult enough to decide upon the truth when weighing the testimony of ordinary witnesses. The defendant who was driving his automobile at the time of the accident testifies that the plaintiff was jaywalking. The plaintiff testifies that he was standing on the sidewalk minding his business when the defendant's car mounted the curb. Difficult as it is to appraise such testimony, jurors rarely need expert help. They can draw on their own everyday experience and knowledge in sifting the evidence.

But the medical expert brings to court his specialized knowledge of a subject about which judge and jury know little or nothing. If the jurors decide that the defendant is at fault—and they usually do—they must then assess damages. They must determine the nature and extent of the plaintiff's injuries and their probable duration. This boils down to diagnosis and prognosis—the acknowledged province of the medical profession.

A greater responsibility therefore rests upon the physician than upon the ordinary witness. Does this touching dependence of judge and jury bring out the best qualities in the medical experts? Like Albert Schweitzer, do they try to bring truth and light into the juridical jungle? Alas, no.

Three types of experts may be called to testify in a personal injury case. One is the family physician or general practitioner who treated the plaintiff, the second may be a specialist called in for treatment or surgery, and the third may be a medical expert who never treated the plaintiff at all. I have little quarrel with the courtroom conduct of the treating physicians. Once in a while a general practitioner who has treated himself to a brand-new x-ray machine may read into his pictures fractures that an x-ray specialist could never discover; but I am

inclined to credit him with good faith. Most civil trials take on the coloration of private fights. Partisanship is infectious and doctors are human. But generally speaking the worst that can be said of treating physicians, family doctor and specialist alike, is that they will not give their patients the worst of it on a close and debatable medical question.

My talk will center on the third type of expert, who can boast of a heavy and sustained incidence of exaggeration and puffing. I shall call them the "testifying experts," rather than medical experts.

The testifying expert is hired by the lawyer, not by the patient. He usually examines the plaintiff, for the first and only time, a few days before the trial. He has just the right degree of diffidence about the lawsuit, just the right air of candor and the flattering technique of taking the jury into his confidence and reducing the recondite science of medicine to a very simple affair.

The testifying expert has developed the courtroom manner as some doctors develop a bedside manner. He will often make flat assertions where his more learned and conscientious adversary will express reservations. Many testifying experts, with appalling consistency, will find injuries difficult for a conservative physician to rule out—such as post-concussion syndromes, low back injuries, herniated discs, etc. The real expert, unversed in rules of evidence, is unable to explain his reservations without running afoul of the laws of evidence. He gives cramped opinions in the framework of weird and unintelligible rules. When thus frustrated he becomes flustered and takes refuge in the style he employs when lecturing medical students. This style is over the heads of the jurors, who are charmed by the testifying expert and regard the real expert as evasive.

This is primarily an indictment of both our professions for inertia and long sufferance, rather than any pervasive measure of unethical conduct. Only a small band of medical mercenaries tailor their testimony to fit the needs of the lawsuit; and they constitute an infinitesimal fraction of the great body of honorable and dedicated physicians practicing in this country. And similarly, only a handful of lawyers hire these experts and plot with them to pervert justice.

There can be little cause for wonder that this small fringe of lawyers retains the small fringe of testifying experts, to the exclusion of the treating physicians. Even if his client has sustained serious injuries that cannot be minimized, why should the lawyer struggle with the treating

physician to make sure his conclusions coincide with the needs of his case? Or why take a chance on the courtroom awkwardness or offensiveness of the treating physician? It is so easy to retain a testifying expert, who will fly with the greatest of ease from a fancy fee to a foregone conclusion.

The defendants—usually represented by insurance companies—cannot, of course, present the treating physicians as their witnesses. Some defendants' representatives, in a realistic endeavor to learn the actual nature and extent of the injuries, retain capable and conscientious physicians to examine the plaintiffs, and if needs be to testify. Others, I regret to say, find it expedient to use expert testifiers, for the same reasons that motivate plaintiffs.

In any event, if the case goes to trial, a battle of experts ensues, to the shame of our professions and to the disgust and bewilderment of the jurors.

The trial judges appreciate how effectively the testifying experts have nudged the treating physicians right out of the courtroom. The judges see the same witnesses ascend the stand time and again, give their dubious hospital connections and then launch importantly into their same stock recitals. Unfortunately the jurors, who serve for only two weeks, are not aware of how frequently the scholarly looking experts testify.

These professional testifiers bring discredit upon both our professions to a degree far out of proportion to their limited numbers. The courtroom in which medical testimony is presented is a showcase for both professions. Irresponsible medical testimony, whether in an accident case, a will contest, a malpractice case or any other form of litigation, carries reverberations far beyond the litigation parish.

The professions are now properly alert to the desirability of taking affirmative measures to promote good public relations. Isn't it just as sensible to drain and cleanse a source of bad public relations?

What is the result of this capture of the courtroom by the testifying experts? There is the degradation of both our professions. There is the increased cost of court processes, for which the taxpayer foots the bill. Without assurance of dishonest medical testimony many cases now in the Supreme Court would never have been brought there.

False medical testimony imposes a more direct burden on the public by reason of bloated settlements and judgments. When both sides sit

down to discuss settlement of a case, either before or after suit is instituted, do you imagine they talk in terms of the intrinsic worth of the case, based on actual injuries? No, they discuss settlements in terms of the defendant's exposure to a verdict at the hands of a jury that is likely to believe the exaggerated claims of a testifying expert. Settlement values are fixed on litigation experience, and litigation experience reflects puffed claims values. So the insurance premiums the public pays are considerably higher because of the perjury content that distorts claims experience.

Although I am medically illiterate, I must ask why a treating physician, whether specialist or general practitioner, is competent enough to treat the plaintiff but not to testify on his behalf. Am I to understand that a doctor may be good enough to treat or operate on a plaintiff—perhaps when his very life hangs in the balance—but that he is not good enough to testify about the injuries he treated? It just doesn't make sense to me, unless as I suspect, the treating expert is not prepared to go as far in the courtroom as is the testifying expert.

This conclusion is fortified by the findings of the Medical Expert Testimony Project, which I mentioned a few moments ago. The project was conceived by Presiding Justice Peck and the Justices of the Supreme Court as a technique to help improve the calibre of medical testimony. Through the invaluable cooperation of Dr. Howard Reid Craig, acting as medical liaison officer for The New York Academy of Medicine and the New York County Medical Society, those organizations set up fifteen different panels of experts, covering all of the usual and even unusual traumatic injuries. In a case of irreconcilable conflict in medical opinion a judge now is afforded the opportunity of appointing an outstanding neutral expert to examine the plaintiff, report and if necessary testify. The Association of the Bar of the City of New York and the New York County Lawyers' Association rendered invaluable assistance in establishing and conducting the experiment.

The project has proven dramatically effective in those cases in which an impartial expert has been appointed and has exercised generally a wholesome and most important effect on the medical aspects of the great volume of personal injury cases. However, since it is a remedy employed on a selective basis, it affects directly and conclusively only a limited number of cases; and so additional measures are required properly to control the testifying expert.

Dr. Irving Wright, at the request of the Medical Panel Committee, made an analysis of 100 of the cases referred to panel experts. He remarked on the failure of the treating physicians to take conservative and accepted measures in the treatment of their patients. For example, there were an inordinately large number of cases involving diagnosis of concussion or fracture of the skull in which no examination of the spinal fluid was made. These and other inexcusable omissions were disturbing to the medical members of the committee. I suggest that many of these indicated measures were not taken by the treating physicians because they simply never had any reason to suspect the injuries which were later attributed to their patients by the lawyers and the lawyers' medical experts. The choice lies between the incompetency of the many or the knavery of the few; and I incline to the latter view.

There will always be some cases in which a non-treating expert must be called. The treating physician may have died, he may have made an erroneous diagnosis honestly requiring correction, or the injuries may be so serious and sharply disputed that supporting testimony is desirable. I am not speaking of such instances but of the generality of cases.

I designedly do not recommend any specific program to curb this expert testimony evil. The important thing is to blueprint the cause and secure joint action by both professions. Nor do I suggest any drastic disciplinary action for what has already happened. These sporadic punitive expeditions soon spend their force and leave the causes undisturbed.

If we once define our mutual problems, we can solve them by cooperative effort. The testifying expert presents just one challenge. There will be other problems. In the spirit best exemplified by our recent cooperation, those problems can also be met.

I repeat what I said at the outset. The role of the physician in court is to help in the search for truth. This ideal role can be made the rule, rather than the exception, only with the cooperation of the decent members of both professions—who constitute the overwhelming majority of their memberships. The professions will have to act affirmatively through their responsible organizations. The honorable physician will have to overcome his aversion to the courts and no longer discourage or shun requests that he testify.

In another context Alexander Pope posed the question neatly over 200 years ago, when he said: "Who shall decide when doctors disagree?"

THE ROLE OF THE PSYCHIATRIST AS AN EXPERT WITNESS IN CRIMINAL COURT*

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State University of New York, College of Medicine at New York City

THIS Academy stands this evening on the firm ground of progressive medicolegal thought on which it has stood for many years. Almost three-quarters of a century ago one of the keenest and most independent jurists this country has ever produced, Judge Edmonton, travelled across the river from New Jersey to appear on the platform of The New York Academy of Medicine and to speak with considerable understanding of the role of psychiatry in the court of law.

In the mid-forties of the past century, American judges were able to improvise with great sagacity and courage as to how the expert testimony of the doctor, particularly that of the "alienist," should be treated. Justice Shaw of the Commonwealth of Massachusetts instructed juries to consider the expert opinion of "these learned gentlemen" (by this he meant us, medical experts) as evidence.

The task of the medical expert witness is a solemn and, more often than not, a painful one: for he who has been trained to heal and to save lives may at some time be forced by circumstances either to contribute to a man's being convicted and sentenced to death, or to stand up and fight with all the power of his service to scientific truth for a poor derelict against whom the law and public opinion are both aroused and uncompromising. It is easy, for instance, to imagine the silent anguish with which the then professor of anatomy Oliver Wendell Holmes testified against his colleague Webster, who had murdered another colleague Parkman, in cold blood.

It is even more difficult for a psychiatrist to testify in a case of burglary, rape, or murder and endeavor to present his honest conviction that the accused, the given burglar, arsonist, rapist or murderer in question happens to be a mentally sick person. The psychiatrist, despite

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his scientific honesty and medical thoroughness, is often looked upon in such cases as the defender of the indefensible. A legendary tradition, based on no facts whatsoever, seems to be firmly established that the psychiatrist is *in favor* of letting criminals go free and uncontrolled by any sanctions. This is not true, of course. But it is an almost universal prejudice prevalent in many quarters of the legal profession and among the public.

This prejudice concerns the psychiatrist in court more than any other specialist; for the psychiatrist remains a sort of diplomated and certified stranger in the court of law. There are a great many historical, cultural reasons why this state of affairs has existed for a number of generations. Without going into details, I may state simply this: the psychiatrist, unlike the surgeon or internist, is not asked merely to give his diagnosis and his reasons for making such a diagnosis. As a matter of fact, until recently the courts were not interested in psychiatric clinical diagnoses at all. The law will accept the diagnosis of malaria, paresis, cancer, as valid, if properly proved. But in cases in which the mental pathology of the accused is in question, the law has established a double standard: medical *and* legal insanity—two different entities. Imagine the court saying to the medical man: Yes, doctor, we agree that the person on trial suffered from appendicitis—but the question that is being propounded to you is in fact this: was this legal appendicitis, or only medical? No lawyer or judge would be so unreasonable as to propound a question of this sort. But when it comes to the question of mental disease, which is still designated in some quarters by the antiquated term "insanity," the law insists: Yes, doctor, but is it or was it medical or legal insanity; or, to put it in other words, is it or was it insanity in the medical sense or within the meaning of the law?

It is this double standard, which is both unscientific and unclinical, that puts the psychiatric expert in a singularly difficult position. The fact that psychiatrists disagree among themselves, which is frequently emphasized as a fundamental defect in psychiatry as a medical discipline, should not be overlooked, but it really should not be given too much importance; as I have pointed out elsewhere, the validity of the law and the integrity of the legal profession are not impeached by the fact that lawyers too often disagree.

The major difficulty lies in the fact that the law keeps on asking the psychiatrist nonpsychiatric questions: we are asked, for instance,

whether the accused was suffering from such a defect of reason that he was unable to distinguish between right and wrong. The psychiatrist, in so far as he is a psychiatrist, cannot undertake to answer questions dealing with purely moral categories. Yet the so-called right and wrong test misleads many a psychiatrist in court. Early in the eighties the legal-moral issues involved in crime became so interwoven with psychiatric improvisations that the best psychiatrists of the day, unbeknown to themselves, served the nonmedical tradition of the law rather than the medical tradition of psychiatry. Therein lay the weakness of the psychiatrist.

This weakness came out clearly at the trial of Guiteau, the schizophrenic exhibitionistic buffoon who murdered President Garfield. Guiteau was executed because he was adjudged sane within the meaning of the law; the judgment of the law was based on the testimony of superintendents of the leading hospitals for the insane, led by the formidable Dr. John P. Gray of Utica State Hospital. Yet it is extremely interesting to note that those medical men who were not confused between legal and medical concepts of insanity, the leading neurologists of the day Doctors Hammond and Spitzka, saw the issues clearly, and to the last they insisted that Guiteau was an insane person. These two neurologists, both eminent medical teachers in New York almost three-quarters of a century ago, did a great deal to mobilize medicopsychological thought and to lead it in the direction of a more clinical and more humanistic forensic psychiatry, the dawning of which we are witnessing only in our time.

Until recently, it was pretty nearly impossible to convince a court that the psychiatrist is the true specialist of a definite branch of medicine. As a matter of fact, it is still possible for a doctor to be admitted to testify as an expert as to the mental condition of an accused without his really being a specialist in the field of psychiatry. Then, too, courts still permit expert testimony as to psychiatric issues even if the alleged expert did nothing but sit for a time during the trial at the side of the prosecutor or the defense attorney without ever having examined the person about whom he is willing to give testimony under oath. It would seem that both the law and the ethical standards of the profession should forbid such practices. As long as these are not forbidden, both justice and medicine will more often than not be done a substantial disservice.

All these and many other defects and deficiencies in the process of psychiatric expert testimony are not a result of either neglect or ill will on the part of the law or of psychological medicine. They are rather a result of the too slow growth of mutual understanding between psychiatry and the law. This understanding has had to go through many hardships; so have criminal law and psychological healing in the course of many centuries. It is therefore a matter of special interest as well as of satisfaction for psychiatrists and jurists in the United States to take cognizance of the turn psychiatric testimony was permitted to make in some of our courts within the last year or so. To call this change which is now taking place merely a turn is perhaps a gross understatement. For here is what is happening under our own eyes in some of the courts of Federal jurisdiction like the Third Eastern District comprising Delaware, Philadelphia and the Virgin Islands, or like the United States Court of Appeals of the District of Columbia. In rendering some of their decisions judges like John Biggs, or Bazelon, began to lean heavily on the clinical data presented by psychiatrists rather than on the shopworn formulae of the right and wrong tests and the other accoutrements of "legal insanity" which had been covered since 1843 by the so-called McNaghten Rule.

A recent decision, rendered on July first, 1954, by the U. S. Court of Appeals for the District of Columbia (Judge Bazelon wrote the opinion with Judges Edgerton and Washington concurring) definitely states that the right and wrong test (and therefore by implication the McNaghten Rule as a whole) no longer corresponds to the realities which are offered by psychiatric clinicians. The opinion referred to, known as the Decision in the Monte Durham case, does away even with the so-called irresistible impulse—as it does away implicitly with such old variants as partial or temporary insanity. Instead, this opinion establishes the following rational and scientific rule: The psychiatrist who comes to testify in a criminal trial no longer needs to straddle between medical and legal mental illness; all he is asked to tell and demonstrate is that the given defendant is mentally ill and that his crime or offense was a direct result of this, his mental illness. This is a serious task that the U.S. Court of Appeals for the District of Columbia has assigned to the psychiatrist. It might require of the psychiatrist that he study offenders and examine them clinically with much greater care than has often been the custom or silent tradition heretofore. But

at least and at last the medical discipline called psychiatry is permitted to take the witness stand with all the dignity, medical and professional, which is due it.

There is great opposition felt even in the District of Columbia to the recent decision in the Monte Durham case. Special committees are looking into the matter now, yet it not only looks as if the "Decision" is here to stay, but it is hoped that various State criminal codes may gradually start on the same open road. If this happens, the old unpleasantness of the "adversary proceeding," in which psychiatric expert testimony has so often been engulfed in criminal courts, is bound to disappear.

To be sure, we still have a long way to go. How slow our progress is we might judge from the fact that the father of "medical jurisprudence of insanity" in America, Isaac Ray, rose to his full scientific and moral stature against the right and the wrong test as early as 1838. He had influenced the great judge of his day, Judge Doe of New Hampshire, and the present New Hampshire law governing the problem—the best we have in this country—was created under the direct influence of the ideas of Isaac Ray. Yet Dr. Ray was seldom if ever quoted by our jurists. He was a psychiatrist, of course, not a lawyer. It is rather significant that the opinion in the Monte Durham case, which quotes a number of contemporary psychiatric sources, quotes most often from the writing of Dr. Isaac Ray. Thus, almost one hundred and twenty years have passed before the court of at least one jurisdiction made Ray's progressive views an active ingredient of a juridical and judicious decision.

We must bear in mind that the roots of the present difficulties and evils with regard to psychiatric testimony in criminal actions go deep into the ages and are also part and parcel of English Common Law, of which we are inheritors. If we bear in mind this perspective, we cannot help but be impressed with the newer trends in certain courts. They bid fair to mark the final and rightful entry of clinical psychiatry into the courts, replacing the old errors and the *ad hoc* improvisations of experts who heretofore were sandwiched in between formulae that no longer correspond to our clinical knowledge and the demands that the psychiatrist tell the court about some legal entity which is only what it has always been—a nonclinical abstraction.

One more word. The recognition of clinical psychiatry in the

court as an expert tool, instead of a contentious plaything between the participants in the given adversary proceeding, brings into the court the conception of the individual as an indivisible unit, the personality as a whole. This is not only in harmony with present-day psychiatry, but also with medical science and biology in general. This is an epoch-making turn in the history of the relationship between psychiatry and the criminal law.

THE LOUIS LIVINGSTON SEAMAN FUND

The New York Academy of Medicine announces the availability of the Louis Livingston Seaman Fund for the furtherance of research in bacteriology and sanitary science. In 1956 $1900 is available for assignment. This Fund was made possible by the terms of the will of the late Dr. Louis Livingston Seaman, and is administered by a Committee of the Academy under the following conditions and regulations:

1. The Committee will receive application either from institutions or individuals up to May 1, 1956. Communications should be addressed to Dr. Wilson G. Smillie, Chairman of the Louis Livingston Seaman Fund, 105 East 22 Street, New York 10, N.Y.

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   a. Securing of technical help.
   b. Aid in publishing original work.
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PARKINSON'S DISEASE: MEDICAL AND SURGICAL MANAGEMENT

*Transcription of a Panel Meeting on Therapeutics**

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Professor of Neurology, New York University Post-Graduate Medical School;
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Panel Members

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* Presented at the Monthly Panel Meeting (Third Series) at The New York Academy of Medicine.

MODERATOR SAMUEL BROCK: Ladies and Gentlemen, we are meeting here this afternoon to discuss Parkinson's disease in its medical and surgical therapeutic aspects. Consequently there won't be much time for any detailed discussions on pathology and physiology, both of which play an important part in our understanding of this condition. Before I throw myself behind this panel of experts and let them do the answering, and worrying about the questions, I think perhaps it behooves me to give you a brief survey of the disease complex known as parkinsonism.

There is much that we don't know about it. It is a disease complex usually divisible into the idiopathic type (sometimes called paralysis agitans), and other varieties which have been called encephalitic, post-encephalitic, arteriosclerotic and a group of mixed parkinsonisms, as it were, that are believed to be due to such toxic effects as carbon monoxide and other poisons. These days we don't see much of any variety other than the ordinary idiopathic or paralysis agitans type.

I cannot go into the pathology except to tell you that it is not a mass lesion type of disease. There is a selective pathology which picks out the basal ganglia, including such structures as the reticular nucleus of the brain stem, the caudate nucleus, thalamus and more particularly below the thalamus, the substantia nigra. It is a degenerative disease, whatever that means. The more we use the word "degenerative" in neurology, the less we know what we are talking about. Suffice it to say, that this disease in its broader aspects seems to be based upon metabolic factors; it may end up by being one of the metabolic diseases of the brain. There are those, however, who feel it has a strong vascular component. Since I mentioned the encephalitic variety, it would appear as if inflammatory factors in certain cases can bear upon the basic pathology. From my own point of view, I look upon the metabolic aspects as perhaps being the most important cause since even when an infection like encephalitis brings about this clinical picture, it sometimes does so many years after the infection and at a time when there seems to be no inflammatory reaction visible on microscopic study of tissue from fatal cases. So there again, it still may be due to an abnormality of metabolism in the brain and in the brain stem.

This cursory survey leads us to the basic symptoms of the disease and I shall only mention them without going into great descriptive

detail. It is a disease in which tremor—usually a resting tremor—is an important element. This tremor is usually more marked in the upper limbs and may be more marked in one limb and start in one limb,—one of the upper limbs usually. It isn't always a resting tremor but is sometimes most evident on intentional movement. Tradition has emphasized the cupped hand and the "pill-rolling" tremor,—one of the important signs of the disease. With this tremor there is what is called rigidity. The rigidity is supposed to be due to dysfunction of the extra-pyramidal motor system. This extra-pyramidal rigidity has certain plastic qualities; one of the most important is the cog-wheel type of reaction which the examiner can elicit by trying to flex and extend the rigid limb. A symptom that is not emphasized enough, though implied in all our descriptions, is the poverty of movement which these patients develop. It has been called hypokinesis and in its most complete form, akinesis. I think this poverty of movement will be especially manifest in some of Dr. Cooper's movies which he will show. This poverty of movement is seen by everyone and sometimes we don't think too much about it. It annoys the patient however. With this poverty of movement goes loss of associated movement. A common and important symptom, seen in the upper limbs when the individual walks, is the defective swing of one or both arms normally seen in each arm in consonance with the forward stride of the opposite lower limb. This defect in swing frequently begins in one limb and is apt to extend to the other upper limb. Finally, as the disease spreads from one side to the other there is a dissolution of erectness, that is to say the erect posture of the individual gives way to a slumped flexion so that the Parkinson patient begins to lose height as it were; you are familiar with that flexed, stooped, bowed posture.

I might say in passing that in the postencephalitic form of the disease the posture has rarely been found to be one of overextension of the trunk. The symptoms do not always occur in equal degree, and there are various combinations. There are also sundry autonomic and other symptoms due to involvement of the hypothalamic structures, as increased sweating and salivation, although salivation is most often due to defective swallowing. Occasionally various arthropathies and pains arise from a combination of causes.

Now then, that is a bird's eye view of the disease; I am not going into the encephalitic variety and sundry other types now because we

are seeing so few of the encephalitic cases.

The pathology of parkinsonism is confined more or less to the nervous system; I know of no somatic stigmata of the disease; animals in nature do not have this disease. The disease usually runs a protracted course.

At this juncture I want to introduce Dr. Lewis J. Doshay, who has the advantage of having spent a good deal of time studying parkinsonism in a special clinical setting. Dr. Kate Constable has also kept a keen clinical eye on this disease working with Dr. Doshay; they are going to take the medical burden on their shoulders, at least as far as therapy is concerned. Dr. Irving Cooper has brought to the therapy of parkinsonism a lot of interesting and forthright data on neurosurgical procedures. These physicians have played a role in our attempts to ameliorate the ill effects of this disease for some time. I am going to ask Dr. Doshay to tell us what he thinks would be the optimal medical treatment of this disease.

DR. LEWIS J. DOSHAY: The early and mild types of parkinsonism in which tremor and rigidity are limited to one side of the body are generally not difficult to treat. Their spontaneous and automatic movements are fairly free. Their facies are not too badly frozen. They smile readily and their speech is resonant and well articulated. The mental faculties are intact. The gait is hampered but little, and the station, posture and balance are well preserved. An occasional patient may suffer embarrassment in the company of friends, or lose a job because of a shaking arm. Most of them, however, do well on a minimum amount of medication. For them we have an ample assortment of remedies. These include extracts of the potato plant family that have been in use for many years.

Among them is hyoscine, which is very widely used in the treatment of parkinsonism. Others include belladonna products (Rabellon, Vinobel and Bellabulgara) with similar amounts of the ingredients, hyoscine, atropine and hyoscyamine and with similar effects and side-reactions. Still others include the one-half per cent atropine solution, tincture of belladonna and the tincture of stramonium. Some physicians prefer the tablets of stramonium.

In addition to the old drugs, we have a large and increasing assortment of new synthetic preparations that have appeared on the market within the past six or seven years.

The most outstanding among these is trihexyphenidyl (Artane).

Experimentation and study of this drug was begun in 1947 and it was placed on the market two years later.

Other synthetics followed in quick succession. Cycrimine (Pagitane) is similar in chemical structure to Artane and its actions and side reactions closely resemble those of Artane. We have patients who have used trihexyphenidyl (Artane) for several years, but when the effects began to wear off, they turned to cycrimine (Pagitane), which is available in 1.25 and 2.5 mg. tablets. Trihexyphenidyl (Artane) with which you are all familiar, comes in 2 mg. and 5 mg. tablets. In addition to these important synthetics for the treatment of parkinsonism, two more have been placed on the market within the past year. Ethopropazine (Parsidol) is an excellent preparation for the control of major and minor tremor. It is available in 50 and 100 mg. scored tablets. In mild tremor cases 25 or 50 mg. t.i.d. is sufficient, but severe tremor cases should be started with 100 mg. t.i.d. and the dose rapidly increased to 600-900 mg. per day. Benztropine (Cogentin) is our most powerful oral antispasmodic. It will counteract rigidity, contractures, frozen states and muscle cramps better than any current preparation. It comes in 2 mg. double-scored tablets. It has a long and cumulative action, hence needs to be used but once a day, upon retiring. During the day, Artane or Pagitane should be added.

There have also been other synthetics added for the control of bradykinesia. For older patients one may use d-amphetamine (Dexedrine) and for younger people amphetamine (Benzedrine). These have come into wide use as cerebral stimulants. We have also borrowed synthetic antihistaminics from the allergists. Diphenhydramine (Benadryl) is a good preparation for the control of mild tremor in some patients. In others it produces disturbing side-effects of drowsiness and mental fogginess, just as hyoscine, and it is hardly superior to the latter. Another useful antihistaminic is phenindamine (Thephorin). Its effect is indefinite. However, many hypersensitive patients who cannot tolerate stronger drugs, because of side-reactions of dryness of the mouth, blurring of vision and somnolence, find some measure of comfort and relaxation in Thephorin, which is gentle in action. To this may be added a half tablet (1 mg.) of Artane, b.i.d. In some respects the action of Thephorin is somewhat like that of reserpine, a calming drug.

Chlorpromazine (Thorazine) is a synthetic motion-sickness drug that finds favorable use in parkinsonism. We refrain from using large

doses, because of the hazard of hepatitis and agranulocytosis and because it could aggravate the Parkinson symptoms. However, in small doses of 25 or 50 mg. upon retiring, we find it very useful as a hypnotic for tense, tremulous and insomnic patients. Its advantage lies in the fact that there is no hangover the following day, whereas with barbiturates there is a sluggishness and drowsiness until noontime, or throughout the day.

For the mild parkinsonian cases we thus have a large store of helpful remedies. In addition, physiotherapy can be used to loosen a rigid arm or leg. In such cases, one treatment a week suffices. Daily active exercises by the patient, under direction of the physiotherapist, are of further help in keeping the body limber.

The real challenge to therapy arises when the rigidity begins to spread from one side of the body, across the neck and trunk, to the other side. When rigidity becomes bilateral and the patient is increasingly slowed up, *then if treatment is neglected*, tragic secondary changes develop that do not belong intrinsically to Parkinson's disease but to factors of disuse. In other words, if a patient does not use a rigid arm, it inevitably becomes tighter and shorter. In due time, fibromyositis sets in. The muscle fibers are replaced by connective tissue which becomes scar tissue. Scar tissue does not relax, nor does it contract. A scarred muscle is difficult to use, hence it is employed less and less. The less such muscles are employed, the shorter they become so that a vicious cycle is formed. Contractures develop that lead to deformities of the hands, arms and legs. At the knees, for example, the hamstrings shorten so that the knees become bent and the body is thrown forward into a propulsive posture. At the ankles, the tendo Achilles shortens, so that the patient is forced to walk on his toes and the entire body is thrown forward into a propulsive and festinating gait. The weight of the trunk is greater than any support it receives from the legs, so that gravity helps to pull the patient down and there are frequent falls and fractures of an arm or leg. As a safety precaution, the family confines the patient to a chair or bed, so that in due time the patient becomes bedridden and invalidism sets in.

Contractures constitute a severe handicap to the Parkinson patient. They can be prevented to a large extent in almost every patient, by rigid attention to proper medication, regular physiotherapy and continual exercise on the part of the patient. Effective treatment would

prevent deformities and disabilities, or at least would postpone them for many years and give the patient free limbs and a capacity for self-care and work.

I have been talking a great deal. I think Dr. Constable knows more about some of these drugs, particularly Artane.

MODERATOR BROCK: *Dr. Constable, will you say anything about the theory underlying the usefulness of the antihistaminics before you get further into it? I mean to say why does Benadryl work?*

DR. KATE CONSTABLE: That I could not tell.

DR. DOSHAY: Would you permit me to answer it?

MODERATOR BROCK: There is an answer, at least a theoretical answer. There are those who think that some of the symptoms of this disease are due to a denervation-sensitization phenomenon in the nervous system which perhaps has something to do with the action of acetylcholine.

DR. DOSHAY: That is the chemical answer, but the physiological answer is that diphenhydramine (Benadryl) makes them sleepy and that is how it quiets the tremor.

MODERATOR BROCK: *Is it purely sleep?*

DR. DOSHAY: When we tested Ambodryl, which has a chemical structure similar to Benadryl, for its effect on tremor, we found that it does not produce drowsiness and that it had no effect whatever on tremor. Benadryl does produce drowsiness and this is probably the only mechanism by which tremor is allayed. We know that during sleep, there is no tremor.

DR. CONSTABLE: I thought that you based the result on the sedative effect of Benadryl?

MODERATOR BROCK: This is a theory that has been put forward. It is highly theoretical.

DR. CONSTABLE: The patient sleeps better with Benadryl and often no further sleeping potion at night is necessary. Most patients will say they had better nights and therefore awaken rested in the morning.

MODERATOR BROCK: *What do you think of Artane? That has been one of the old favorites.*

DR. CONSTABLE: I believe that trihexyphenidyl (Artane) is one of the best drugs that we have had so far. First of all, it is non-toxic. There are practically no side effects that are difficult to tolerate or become used to, and it is effective. It certainly allays the rigidity of Parkinson's extremely well. It does not do much for the tremor but the rigidity

of Parkinson's disease which is a very handicapping symptom is practically always relieved by Artane, even in fairly small doses. Artane also does not cause mydriasis as some of the other drugs do. The patient is able to read and is not disturbed with the drug. It does not cause as dry a mouth as most of the other drugs. The patients do not complain of being dried up at night and being dried up during the day. It also has a general euphoric effect upon the patients. They will tell you their morale is better. They feel more interested in things. They not only sleep better but their appetite is better. Many patients who have had chronic constipation for years, whether independent of Parkinson's disease or secondary to it, will tell you that that condition has been improved on Artane. I have had many patients tell me that for the first time in years they have not had to take cathartics and enemas after having been started on Artane.

MODERATOR BROCK: *Dr. Constable, supposing you have allayed the rigidity, have you ever noticed that sometimes there is more tremor as an escape of the hampering effect of the rigidity?*

DR. CONSTABLE: On the other hand, I think the tremor is secondarily improved when the rigidity is relieved.

MODERATOR BROCK: *Given a case of non-relief, so to speak, of the tremor or relative non-relief as compared with the alleviation of their rigidity, what would your secondary drug be? What would you use with the trihexyphenidyl (Artane)?*

DR. CONSTABLE: First of all, I would try cycrimine (Pagitane) or benztropine (Cogentin), or phenindamine (Thephorin) or diphenhydramine (Benadryl). Frequently the combination of one or other of those drugs will help the tremor as well as the rigidity. Then of course one can always fall back on hyoscine if one has to, though I practically never use hyoscine any more.

MODERATOR BROCK: *May I ask you this, have you any special way of attacking the thing which has been called the hypokinesia, the poverty of movement?*

DR. CONSTABLE: I attack that by physiotherapy. First of all, I think that you must build up the patient's morale and you must start him on a regimen of doing something for himself. Many Parkinson patients with rigidity are perfectly willing not to talk, just to sit and then not even eat; they will wait to be fed. The sooner you teach them that the important thing is what they do themselves, the sooner your drugs

will help them and will put them in a position in which they are more amenable to physiotherapy. Physiotherapy is very important and not only in the clinic or in the department where they are under active treatment, but it must be carried on at home. They must be taught to have a regular regimen that they must go through,—exercises two or three times a day and if they are at home they would do much better to carry on such a program than to sit idly and wait for the day to be over. And that unfortunately, is what happens to so many Parkinsons.

Another thing, I feel that the person should continue to work. If it is a person with a job he should continue to work on that job. If it is a housewife she should learn to do things for herself and continue doing housework, even if it be a matter only of washing dishes, and making beds. It is important to have these patients try to continue their normal activities and not have others do for them, thus causing them to become more and more immobile.

MODERATOR BROCK: *Dr. Constable, in line with what you have just said, do you think we as physicians have been a little remiss in not supervising the program of their daily activities?*

DR. CONSTABLE: I certainly do.

MODERATOR BROCK: We have cast them adrift by just giving them pills or delegating a physiotherapist to come in and give them a bit of massage and so they drift on their own.

DR. CONSTABLE: Yes, I agree. I think many physicians will say there is nothing that can be done. The attitude is, if a patient has Parkinson's disease,—"Go home and sit". The patient leaves the office depressed, with a feeling that there is no hope. One of the first things I say to a Parkinson patient is that he has a disease which cannot be cured; but that we can help his symptoms, we can make the rigidity and tremor less and help him walk better and do things better, not in the way he used to do them, but we can bring about improvement and, if he keeps working at it himself, he will continue to hold that improvement. One has to see these patients frequently and give them this mental stimulation; one has to do it regularly and perhaps a busy general practitioner has not the time to do so, and we do not have enough time in our clinics. We have to see too many patients. If I see three Parkinson patients in a morning, I spend considerable time with each. I think they are getting much more than medication. Of course one has to give them medication also. But they need psychotherapy sorely; one has to be

a psychiatrist as well as a neurologist in treating a Parkinson patient and his family.

MODERATOR BROCK: It is a kind of morale-building and is essential.

DR. CONSTABLE: Indeed it is. It is really psychotherapy that you use both for the patient and the family as well. One finds a husband who does everything for his wife, puts on her shoes, buttons her dresses and hands everything to her. One of the things I emphasize is the value of letting the patients do things for themselves. For example: let them try to put on a coat alone, to struggle with it. By so doing, you are not being unsympathetic but are giving them an opportunity to do things for themselves and exercise their own muscles and to continue their independence of others.

MODERATOR BROCK: You will notice, ladies and gentlemen, that thus far I have not questioned Dr. Cooper about the medical aspects, not out of discourtesy, but I am looking to him to present the surgical situation and its therapeutic effects. *But before I do that I think it might be in order if we asked the audience to quizz my medical colleagues here on matters relating to the medical treatment of this important disorder, so I will entertain some questions from the floor.*

One questioner asks: "What are the maximum doses a day of 1) Rabellon, 2) Artane and others?"

Dr. Doshay, do you want to answer that?

DR. DOSHAY: Rabellon comes in a double scored tablet. The full tablet has a half milligram of the ingredients of belladonna, that is the active components of belladonna. Some patients, since it is double scored, will break off a quarter of a tablet and take a quarter of a tablet three times a day. Some older people who are sensitive, who find the slight mental fogginess from Rabellon disturbing to them, take a quarter twice a day. On the other hand, there are elderly people, even patients of 75-80, who readily tolerate 3, 4, or 5 Rabellon tablets a day. I have one patient who has been taking 36 tablets of Rabellon every day for the last six years. If he takes one tablet less he feels he is going to collapse, that the symptoms would not be held in abeyance. There is a tremendous range in dosage with Rabellon, but usually patients will take between a half a tablet three times a day to about four, five or six tablets a day.

MODERATOR BROCK: *Dr. Constable, what about the maximum doses of trihexyphenidyl (Artane)?*

DR. CONSTABLE: The maximum doses:—we have several patients in the clinic taking 10 mg. four times a day. That is a large dose. I have others who take 5 mg. four or five times a day. I should say the post-encephalitic patients will tolerate and need between 25-30 mg. while the arteriosclerotic usually requires only 2 mg. three or four times a day. I do not find anybody who cannot tolerate that much.

MODERATOR BROCK: *The same questioner wants to know: What should one do when the arm becomes so rigid at times that even an attendant is not able to raise it? Then the arm becomes painful. What should one use when a patient has an attack of sweating when he loses hundreds of grams of water in sweat? How do you treat severe decubitus?*

You treat decubitus along various lines, not pecular to Parkinson's. Dr. Constable and Dr. Doshay, what about sweating?

DR. DOSHAY: All the anti-Parkinson belladonna drugs or belladonna-like congeners, that is the synthetic preparations that work like belladonna, trihexyphenidyl (Artane) or cycrimine (Pagitane) counteract sweating. They all dry up saliva, tears and perspiration. However, patients who have severe or major tremor will sweat from excitement; they will also have emotional vasomotor changes. It is a difficult problem to control their sweating. We have, for example, a physician, from Buffalo whom we admitted four weeks ago who was down to 126 pounds. He was unable to move or talk. He had a violent tremor and sweated profusely. We placed him on ethopropazine (Parsidol). He has improved a great deal. It has quieted his tremor. We had to go up to about 500 mg. a day. Warner-Chilcott recently put out Parsidol in a new form, 100 mg. size tablets. All you have to give is five tablets a day (i.e., 500 mg.). His sweating became controlled within one week, whereas before he was sweating buckets from the violent shaking. He has not sweated now in the last three weeks since we controlled the tremor with ethopropazine (Parsidol). I don't say you can do it with every patient. It is an individual problem. Some patients cannot take ethopropazine because they feel dopey and drowsy. They complain of blurred vision and inability to think.

MODERATOR BROCK: *What about the extreme rigidity, Dr. Constable, that this questioner propounds, what do we do about it?*

DR. CONSTABLE: Increase the drug if the patient can tolerate it and prevent the contracture from occurring is the best therapeutic approach.

MODERATOR BROCK: *Another questioner asks and I think you may have the answer, Dr. Constable, "Is glaucoma a contraindication to commencing treatment?"*

DR. CONSTABLE: Not for trihexyphenidyl (Artane).

MODERATOR BROCK: *"If glaucoma comes on after the patient has been on Artane therapy for some time do you keep on?"*

DR. CONSTABLE: I keep on with that and I think everyone feels it is perfectly safe to do that.

MODERATOR BROCK: *I am also given this question: "Weakness and debility are distressing symptoms that I find difficulty in treating. What recommendations can you make?"*

DR. CONSTABLE: That of course is a problem. You can use amphetamine or d-amphetamine, or one of the stimulants.

MODERATOR BROCK: *Would any of you gentlemen say anything about the thyroid gland as a participant in this matter? It has been dragged in by the tail. It hasn't any tail but there have been those working with hyperthyroidism in parkinsonism. Have you had any experience with it?*

DR. CONSTABLE: No. Is that on the basis of loss of weight?

MODERATOR BROCK: Yes, some Parkinsons lose weight, sweat a lot and perhaps even have an elevated basal metabolism.

DR. CONSTABLE: It is hard to do a basal metabolism on a patient with tremor.

MODERATOR BROCK: The diagnosis may be based further on the radioiodine uptake in suspicious cases.

DR. CONSTABLE: I have not seen any.

DR. DOSHAY: There are many patients who can take a small amount of thyroid and they sometimes do it without our advice, because while going to the neurologist, they are also seeing the glandular specialist and the internist; they come to us taking a grain of thyroid each day,— some of them two grains, some a half grain,— as a substitute for d-amphetamine (Dexedrine) as a stimulant to pep them up and to increase their metabolism; particularly, the lethargic, the sluggish and the akinetic patients may have a low basal metabolism of -30, -40 or -20. Most of them have a slight reduction of metabolism, -8 or -10.

DR. COOPER: I had an opportunity recently to talk to Dr. Schwab at the Parkinson Clinic at Harvard. They have treated some people, as you mentioned, with high basal metabolic rates, marked sweating and

considerable debilitation, with a radioactive cocktail to knock out the thyroid. It seems to help the symptoms but not the major symptoms of parkinsonism.

MODERATOR BROCK: *I was referring to that group. I am glad you brought that out.*

DR. COOPER: I discussed it with Dr. Schwab. He does not feel it is the treatment for parkinsonism but for a few of the special symptoms.

MODERATOR BROCK: *I take it they have a suspicion that the thyroid is under a whip.*

DR. COOPER: Because of the Parkinson symptoms.

MODERATOR BROCK: *Dr. Constable, do you think a Parkinson patient should be told the name of the disease?*

DR. CONSTABLE: Yes, they are going to know it anyway. You might as well tell them. You have to tell them the truth about it. It is a disease in which they are not going to recover completely, never going to get absolutely well.

MODERATOR BROCK: *I am asked, "Has unilateral burning of the body and extremities been seen as part of Parkinson's syndrome? If so, how is this treated?"*

DR. DOSHAY: Paresthesias do occur in some patients. We see them, especially in bilateral situations. They complain of burning of both legs, burning of the right arm and the left leg, and it is difficult to understand the mechanism.

MODERATE BROCK: *It might possibly be due to involvement of the thalamic region.*

DR. DOSHAY: Degeneration? It seems that people of that type respond nicely to reserpine, or Rauwolfia whole root compounds.

MODERATOR BROCK: *I am asked to elaborate further on the mechanism of diphenbydramine (Benadryl) activity. All I can say is that Magoun and Ward, both neurophysiologists of eminence, have been investigating this situation and have presented the idea that Benadryl may act by counteracting the release of cholinergic ferments (enzymes) in denervated tissues in the reticular substance of the brain stem, which is, by the way, believed to be the place where the tremor begins. That is what Ward calls the tremogenic area. By virtue of such counter-effect the value of Benadryl may be explained.*

My two colleagues here tell me, and they may be right, that it is just a matter of sleepiness and no such highly chemical explanation as has

been propounded by these authors. Does that answer your question about the Benadryl?

QUESTIONER: Yes.

MODERATOR BROCK: *I have been asked: "What is the role of trauma in the etiology or the aggravation of Parkinson's disease?" Having had a kind of "traumatic background" myself, I will answer this.*

MODERATOR BROCK: Most neurologists who have given it thought, especially S. A. K. Wilson, believe that trauma does not play a part in activating parkinsonism because in the first place the complex of lesions is deeply placed in the brain stem and high up in the brain. For trauma to have any effect on this area would presuppose a very severe trauma likely to be fatal. What happens of course in people who are litigation-minded is that they hurt an arm and then they begin to see that they have a tremor and a little rigidity in that arm and a lawyer gets an idea and says, "The brick that fell on John Doe's hand caused Parkinson's disease in that hand." Well now that is obviously so far-fetched and fantastic as to be pure invention. The one exception is in encephalitic cases in the younger group, in which severe head trauma can possibly aggravate the disease, even possibly through emotional factors which do play a part in the disease picture and its activation. But by and large my experiences with trauma in Parkinson's disease make me believe that it does not seem related to it. Most of the authors of stature on this subject have the same feeling,—that it is not part of the picture.

The last question before we pass to the interesting surgical side, "Is caramiphen (Panparnit) a valuable drug in parkinsonism?"

DR. DOSHAY: May I answer that? Caramiphen (Panparnit) is now available on the market in 12.5 and 50 mg. size tablets, in which dosage it is no longer as toxic as it was when we first studied it in the 250 mg. size. By the same token, it is not as effective as it was. The post-encephalitic patients have high tolerance, hence were able to take 6 or 8 tablets of the 250 mg. variety a day, without suffering any difficulty. However, older people taking large doses complained of dizziness, mental confusion and nausea, and some vomiting. So, we discontinued its active use. But it can be used in post-encephalitic cases, where it is safe, and the tolerance is high. I would not use it in the older people, because we have better drugs now.

MODERATOR BROCK: The meeting leaves the medical side of this problem now and it devolves upon Dr. Cooper to tell us his interesting

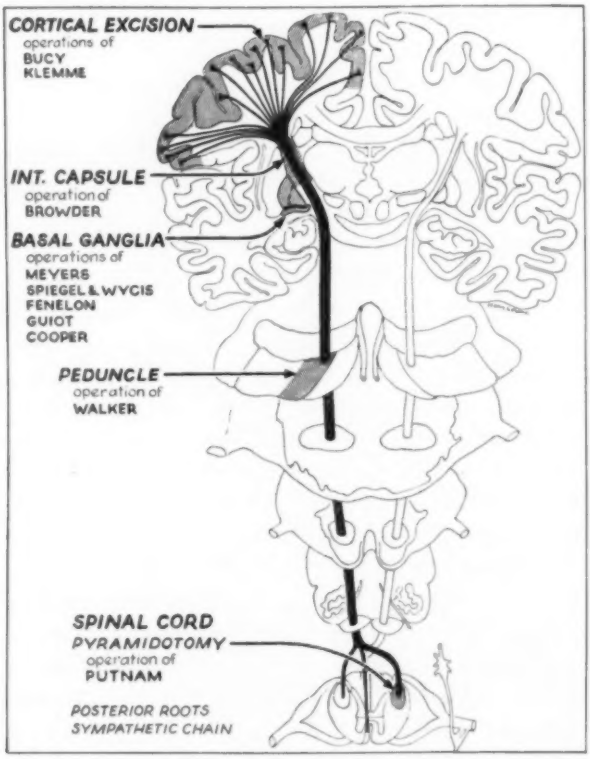

Fig. 1—Diagrammatic representation of various neurosurgical approaches to the therapy of parkinsonism.

adventures in his neurosurgical approach to this disease. His discussion and movies are of transcendental interest.

DR. IRVING S. COOPER: As usual in approaching the problem of parkinsonism the neurosurgeon has been held at bay until time is running out.

In the past, medical treatment has, of course, controlled a great many of the Parkinsonians. Nevertheless, even with medical therapy and psychotherapy and physiotherapy, which is seldom applied as it is applied in the hands of Dr. Doshay and Dr. Constable, many people have become helpless and deformed and disabled. I think that the reason that

we have not heard more about these deformed and helpless Parkinsonians than we do, compared with multiple sclerosis patients, for example, is because that when they become deformed they often lose their voice and are silenced. Thus, they are a pitiful group who have been literally unable to raise a voice in their own behalf and have become hospitalized in chronic disease institutions at a relatively early age in many instances. At any rate, because of that and because of the ineffectiveness of medical therapy in the severe cases, many surgeons have approached the problem with a view to seeing what they could do about some of the signs and symptoms. The surgical therapy of parkinsonism has progressed as our knowledge of the nervous system has progressed. I have a few slides to show before the movie, just to tell you what has been done by others as well as by myself in the disease.

May I have the first slide? (Figure 1.) Without discussing too much the physiology of the disease, the cortex was the first site available to neurosurgeons. Klemme, Bucy, and others removed part of the motor cortex in an effort to stop tremor on the opposite side. They were successful in stopping tremor in direct proportion to their success in producing a hemiplegia. The actual mechanism of tremor or rigidity in parkinsonism was not attacked by that operation. Although it played some part in the understanding of the physiology of the disease, I do not think it has ever been seriously considered as a therapeutic maneuver. Dr. Browder went deeper into the brain and cut the internal capsule which usually produces a hemiparesis on the opposite side and reduces the Parkinson tremor accordingly.

I think it is symbolic of the terrible condition in which many of these Parkinsonians find themselves, that the surgeons were able to find the courage to do the things that we have tried in this disease. Because hemiparesis would alleviate tremor on one side when the cortex was removed, surgeons wondered about other ways to produce a hemiparesis which in some cases would be preferable to the tremor. The operation of pyramidotomy was devised by Tracy Putnam, who as you know, has been a courageous investigator, in an effort to stop the tremor and rigidity, but the tremor was abolished only to the degree that hemiplegia was produced and rigidity was unaffected or made worse.

This crude diagram also demonstrates the so-called extra-pyramidal nuclei or basal ganglia. The one I want to call attention to is the globus pallidus, because about 1942, in a series of investigative operations,

Fig. 2—Cerebral arteriogram demonstrating the anterior choroidal artery.

Russell Meyers cut the fibers emerging from the globus pallidus and in some cases relieved the tremor. The operation carried a high operative mortality rate and has not been adopted by other surgeons. It was performed as an experimental procedure in the hands of Meyers, who is one of the most capable and reliable reporters in the country. His efforts stand as an important piece of physiologic work although the operation has never been utilized to any appreciable extent.

Others then tried to approach that region. Spiegel and Weiss with a stereotaxic instrument have coagulated the ansa lenticularis. In some cases, although not the far-advanced bedridden cases, they have been able to eliminate tremor on the opposite side of the body without producing a paralysis.

Once during an operation on a Parkinsonian patient I happened, inadvertently, to ligate the anterior choroidal artery. We stopped the

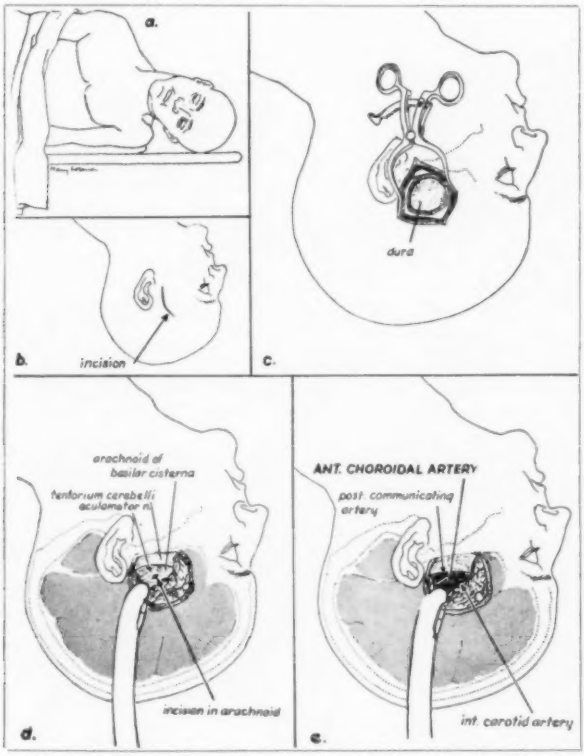

Fig. 3—Surgical approach to the anterior choroidal artery.
(a) Position on surgical table.
(b) Incision.
(c) Craniectomy in subtemporal region.
(d) Elevation of temporal lobe to expose the basilar cisterns.
(e) Exposure of the anterior choroidal artery which is then occluded by electro-coagulation.

operation to see what would happen and happily the patient was free of tremor and rigidity on the opposite side without any paralysis, which led us then into the operation of anterior choroidal artery occlusion. This shows the anterior choroidal artery in an arteriogram (Figure 2).

Figure 3 demonstrates the way we approach the anterior choroidal artery. The rationale of the procedure is that by occluding that anterior

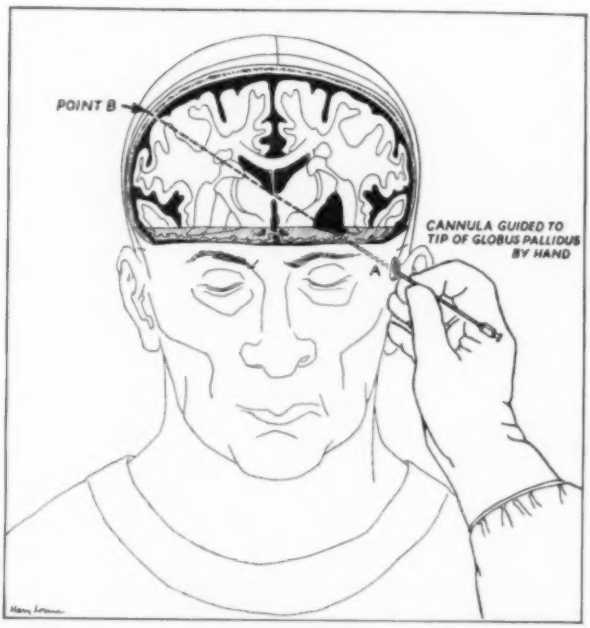

Fig. 4—Method of placement of cannula into the globus pallidus. This enables the surgeon to inject procaine or a neurolytic agent into this region of the brain.

choroidal artery one can infarct part of the globus pallidus and certain related extra-pyramidal connections and relieve tremor and rigidity on the opposite side. I have done this 52 times with a mortality of 10 per cent. Of the cases, two-thirds of the patients are free of tremor and rigidity on the opposite side, as will be demonstrated in the subsequent motion pictures.

In the early part of the series, the operation carried a high mortality, a marked postoperative morbidity and was extremely trying. Those who have tried it in a small series have all had similar experiences. As with all procedures, as we gained experience it has become safer and although it still carries considerable risk in selected cases, as I will show you, it has the opportunity of doing considerable good to the patient, and in some instances of far-advanced cases has produced rather remarkable results.

Fig. 5—X-ray taken during surgical procedure of chemopallidectomy. This demonstrates the intracerebral portion of the cannula.

Exploring other avenues, it occurred to us, once we had convinced ourselves that the globus pallidus could do this trick if it were destroyed, that we could place a cannula in the globus pallidus through a simple trephine opening, because it is a short distance, 4.5 cm., beyond the cortex, and could then inject procaine into the globus pallidus to see if we could alleviate the tremor on the opposite side. We postulated that if we could locate the area with the procaine we could then inject absolute alcohol into it and have a benign, simple operation that could contribute to the welfare and comfort of the patient. We have done

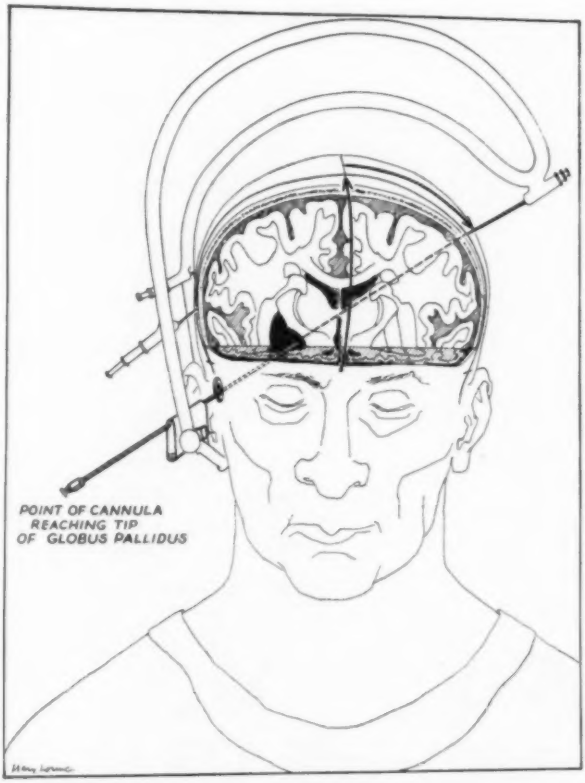

Fig. 6—Demonstration of recently developed pallidectomy needle guide which facilitates placement of the cannula into the globus pallidus.

that 43 times. Again we have two deaths for a 4.5 per cent mortality, one hemiplegia and about 65 per cent of patients have had a remarkable relief of tremor and rigidity. The longest now has gone over a year. The longest in my series of choroidal operations has gone two and a half years, with maintenance of the original operative improvement.

Figure 4 demonstrates the route of injection of the globus pallidus and Figure 5 is an x-ray taken during operation. As you can see, we have been able to put the catheter exactly where we planned to put it by a simple technique. At any rate, it is in the globus and the procaine

in this case alleviated the tremor and rigidity on the opposite side, and alcohol increased the effect and it has now, in this particular case, persisted for eight months.

I want to say this, that there has been a tremendous bona fide, scientific, honest skepticism about whether tremor and rigidity can be relieved without producing a paralysis; or, if it is relieved, whether it was done by psychotherapy, and, if it was not done by psychotherapy, whether it will last.

We will show you some of the motion pictures of these cases, and I will say that every case in my series has been examined by many investigators. I think that now that some of our cases have been followed two years or more, and that we have a large series of almost 100 cases, with a large proportion of patients who have remained well a long time, and having chosen these cases from among the most seriously handicapped patients imaginable, who had not responded to all the medical therapies which we have discussed today; I believe these films demonstrate that there is a new hope for these people. This hope lies not necessarily in surgery for all cases, but in our understanding the physiology of the disease and in developing new medical therapy which may one day produce comparable results. The film runs about 24 minutes for all of it, if you cannot stay you can allot what time you wish.

This first case is representative of far-advanced, debilitated type of Parkinson's that we have done in this series. As far as I can see, when they reach this point, they don't do well on medical therapy. This patient was 42. He developed encephalitis at age 15. He was 100 per cent incapacitated by age 17. He had a nurse for 25 years as an attendant. He was seen by a great many neurologists during those 25 years, had every form of medical therapy imaginable, but had reached this helpless and debilitated stage. He could not speak. He had a masked face, tremor of lips and chin. He was referred by Dr. Walter Freeman, Professor of Neurology at George Washington University. He had intractable tremor on both sides and the deformity of his left hand was marked and could not be reduced under sodium pentothal anesthesia. The thumb was stuck in the palm next to the little finger. At operation, the right anterior choroidal artery was occluded. The patient is seen in this film the next day, and the left extremities are completely free of tremor and rigidity on that side. He can already bring the thumb out and moves the extremities well and has no evidence of hemiparesis. I have pictures

of this man taken every month but time does not permit, so here he is a year later. Within three months that patient's deformity of his left hand reversed itself completely without any physiotherapy. He could walk, gained 30 pounds, became completely independent for the first time in 25 years. That is the hand that was deformed and, as you can see, it has become completely normal. I take exception to the idea that the deformity is due only to contractures of disease. I think this deformity was a fixed type of deformity which reversed completely after the neurologic lesion produced by operation. As a matter of fact, I had no idea that it would reverse to that extent. Although we have not operated for the right side and he still shakes on the right, he is able to tie his shoe laces, which is a pretty good act, with this left hand that was previously deformed. This man has no tremor or rigidity on that side. He has been examined by many investigators, as you can imagine. Here he is 18 months postoperatively. My feeling is, no matter what the future of surgical therapy in this disease, that the reversal of this type of deformity must have some significance for the treatment of this disease in the future. Here is the hand 24 months and still normal. We all know that there is always a possibility that it may recur. Parkinsonism has always been a progressive disease. No one can predict whether this or any of these cases will recur. Here is this man; he has had 24 months of life which he had not had for 25 years previously. He gets on a bus now in New York and goes to the movies alone. He gets dressed by himself although it takes him an hour to do so, and feeds himself, after having been a nursing problem for 25 years.

This next patient in the film was a lady referred to us by Dr. Francis Grant of Philadelphia. We followed her for a whole year before we would let her submit herself to this operation. During that year the hazard became less and the prospects of helping her became greater and she became disabled despite what I thought was good medical therapy, in the hands of medical doctors. There was typical dystonic deformity, rigid deformity on the left side, but nothing like the patient preceding. I think this lady falls into the so-called idiopathic group. The first patient fell into the post-encephalitic group. As you see, she has a marked petit pas, can barely walk and had an attendant as well as a housekeeper at home. She had rather marked tremor, stooped gait, and masked face. I think this is the classical picture of parkinsonism which has not responded to medical therapy, although the patient was not bedridden.

She is an intelligent woman and could understand the liabilities and risks of the procedure. I occluded her right anterior choroidal artery and here is a motion picture of her four months later. She was one who had a rather uneventful postoperative course and was able to leave the hospital in three weeks' time. Many have a much more stormy course and are in the hospital for a much longer period of time. You see she shakes only on the right side. Apparently, when the picture was taken, somebody told her to swing the arms, which she is trying to do a little too hard. Actually she does swing the arm and she is independent, has gained 30 pounds, has planted strawberries in the yard and drives a car and shakes only on the non-operated side. As you can see, her facial expression has changed. Her medical therapy was trihexyphenidyl (Artane) preoperatively and because she still has a parkinsonism on one side she has been kept on it but shakes only on one side. She is seen here a year later and she still shakes only on one side, without any evidence of hemiparesis, without any hemianopia that we could determine.

This next case is the most severely vegetative patient that we had in our series. This man was 46. He was completely incapacitated 17 years earlier, and for ten years was in bed, taken care of by his mother in the hills of West Virginia. He had the maximum of medical therapy. He had been seen and followed by Dr. Lyle Gage of Bluefield Sanitarium for seven years before. He was sent to us completely helpless and immobile due to rigidity at that time and was the most helpless individual we have seen. He was actually sent to the Institute of Rehabilitation to Dr. Howard Rusk. Extensive rehabilitation and psychotherapy were tried. They have a series of tests called the activities of daily living, of which there are 127 rudimentary simple tests. This man could not perform a single one of the 127 and I believe he holds the record. He could not lift his hand to pick up a glass of water, could not turn over in bed and could not talk. As you see, he cannot walk and is about as helpless as a patient can become. This was a completely incommunicado state. We had no idea what type of person lurked behind the rigid body which encased it. He is 46 and looks older. His tremor is not enough to incapacitate him but he was as rigid as it was possible to become. Interestingly enough being as rigid as that he now has no deformities. This is a patient who, if merely being bedridden would bring on the deformities, I think he would have had them. Here is a motion picture three weeks after operation on the left anterior choroidal artery. There

is relief of tremor and rigidity with return of automatic movements on the right, but no weakness. He could talk, although barely. He turned out to be quite a pleasant chap, helped do jobs on the ward and was elated over being able to move. He can write with his right hand and he could do so within five days after operation. Occasionally, in some patients, there seems to be a small degree of ipsilateral improvement, that is, on the same side as the operation. Here he is 12 months later. His face is changed to some degree. He can shave himself, although I would not want him to shave me, but he can do it, and as Dr. Doshay pointed out, it means a lot to people to be able to help themselves once again. After the operation this patient was sent back to West Virginia, was not treated with physiotherapy or psychotherapy, except that he had his head opened, if that could be called psychotherapy. This man remained quite rigid on the left side and we recently operated on the second side, with the second operation which we mentioned. I don't yet have postoperative pictures on the second side, but he is one of the most successful bilateral cases that we have.

Here is the other type of problem, the problem that heretofore has been considered the only reasonable one to approach with neurosurgery. This film demonstrates a 49 year old man who had this disease for seven years, for the last five of which he could not work. Obviously he is not incapacitated, but he is a roofer by trade and he could no longer do the work. We did not undertake any patients of this type for the first year of our investigation. The operation was just too dangerous. However, after being satisfied that there was a chance to help him and once he and his doctor were fully aware of the risks involved we operated upon him. As you see, his problem, although he has some rigidity, is primarily tremor. We did the operation under local anesthesia because it is safer. Many people who had been skeptical of the procedure ventured the opinion that improvement would come from hemiparesis, but it is obvious from this film taken immediately after operation that this person has good results and they are in no wise dependent upon weakness, since tremor is gone but motor power persists. As a matter of fact, a month after operation this man drove his truck, returned to being a roofer, which I understand is what he is doing at the present time. We have followed him now for about 13 and one-half months. I have no idea whether or not he will recur. I would like to make that plain. That is a hazard of any type of surgery or any type of treatment. As the

moment he has not recurred. He is quite remarkably free of tremor, without any deficit that we can determine, and appears normal in all respects.

Here is another case. The reason we are showing quite a few cases is that I think it is necessary to show that these findings are not accidental; that it didn't happen to one or two people because we ventilated their head or affected them psychologically. This man was also done under local anesthesia. Here is the hand immediately postoperatively. He is entirely free of tremor and able to move his hand well. This is the incision. This is the patient five days postoperatively. This patient also had a much less stormy postoperative course than many; particularly the vegetative, debilitated post-encephalitics. This patient, although completely free of tremor at rest, when he is busy and occupied does demonstrate a little tremor in the right hand if he becomes emotionally upset. This case will be the last one in this series and then I will just show one case of chemopallidectomy. This is a young man, who is 38, post-encephalitic and 100 per cent helpless. He had been at most clinics in New York City. Many of you may recognize him because he made the rounds. He is from Brooklyn. His hands are deformed and he is absolutely immobile. We followed this man for a year before we accepted him. He had as much physiotherapy as it is possible to give. He had trihexyphenidyl (Artane), cycrimine (Pagitane) and all types of drugs. He remained in this condition. He could not close his fists, which is what he is trying to do in this film, and he is as stiff as a board. He is trying to reach for that glass of water but cannot. When it is put in his hand he is trying to bring it to his mouth. He cannot. This is the type of patient that at the moment is filling many a bed in a chronic disease hospital, in which, admittedly, anterior choroidal artery occlusion carries a considerable risk compared with medical therapy but in whom I think, in selected cases, the risk is often justifiable--more particularly in the face of possible marked improvement. I think that depends a lot on the individual patient, on the surgeon who might be willing to attempt the operation, and the doctor who has been looking after the patient, as well as his family. This man cannot walk, as you can see. We occluded his left choroidal artery, again under local anesthesia, which we think is extremely important. We would never again use general anesthesia in this type of patient. He had what appears to be complete relief of tremor and rigidity on his right side. The left side, as you see,

still is useless to him to any large degree. There he is attempting with his left hand to unbutton a button and cannot do it. With his right hand he can, which is a pretty fine technique to demonstrate the ability to use the hand. He can walk. He can dress himself and feed himself. By this time he was able to push other patients in their wheel chairs around the corridors of the hospital. Although he still has parkinsonism he is quite a different person than he was before. I think the difference in facial expression is obvious. The fact that the hand is still free of tremor and rigidity six months after operation is obvious. He has good face movements. I think some cases of hypokinesia are due to rigidity. This is such a case. I am sure that there are other cases in which the hypokinesis is due to involvement of other basal ganglia and may be on a hypothalamic basis or some other basis in which it is not due to rigidity. I am sure that if a surgeon operates on such a case and expects to relieve the akinesia he will report failure. If he operates on such a case as this one he will relieve it surgically. As you see some prefer to shave with an electric shaver, some with a safety razor. We only show this to demonstrate that the movement which has returned to this man's extremities can be translated into useful, everyday living and that this man is now completely independent. He is the father of two small children and he is now returned to a useful life in his community and I hope that it will be permanent. Of course there is no way of knowing until we live long enough to find out. You can see that his right arm swings. His left arm does not. The left arm shakes, the right arm does not. This man is not anxious to be operated for the second side and I am not anxious to operate him because he is now independent and I don't think he is justified in taking the additional risk of another operation.

This portion of the film demonstrates chemopallidectomy. It is an operation which we started so that we could have something to offer to the aged Parkinsonians. It looks as though it may go further than that. Here is a man who is 46 and we chose to do a chemopallidectomy. His problem was largely tremor. As you can see it is impossible for him to hold the newspaper and read it because of his marked tremor. This patient was not vegetative as you see,—he still retains a sense of humor. He could still walk but he had violent tremor and rather marked rigidity; on the left you see his hand has an early deformity. His toe has a deformity on the left and he complained bitterly of a rigid cramp in his left calf. You see that he drags the left leg when he walks but

he can walk. This shows how we do this operation in a sitting position. This is a home made chair with a cassette holder. These patients have to submit to operation in a sitting position under local anesthesia. There he is. We are making a more comfortable chair but these patients were willing to pioneer the procedure. We operate on the right side for the left extremities. This is where we make the trephining opening with landmarks which we have set out and measured beforehand. We are shooting at the landmark at the opposite side of the head, which is a technical matter and described in a technical journal, and we don't have to go into it here. Immediately upon putting a drop of procaine in the globus pallidus, the hand stopped shaking as you can see. The photographer went around to take it. He is now back around at the scene of operation. We are injecting a quarter of a cc. of absolute alcohol in that region. The site of the catheter is confirmed radiographically before any injection is made and you see now only shaking on one side, but he is not paralyzed on the left side, as you can see, and he is free of rigidity, whereas he still retains tremor and rigidity in the right extremities. I think that the graphic demonstration of the relaxed extremity on the left compared with the right is evident. The patient is able to take a drink of water during the operation. He is able to respond to all commands and help us. For the first time he can cross his leg and he stated that the cramp was out of his leg immediately upon cessation of tremor and rigidity. Interestingly enough, it was this relief that he was most grateful for.

Because tremor fluctuates we shoot enough film to show that the disappearance of the tremor is permanent. This is the catheter which we allow to remain in the brain for about five or six days so we can make a second small injection of alcohol to insure permanency of the lesion. This is a man who was able to get up and walk away from the operation. I would not want you to think that many can do that but he did. We took a picture when he got back to his room and he is still free of tremor and rigidity on the left. Here he is a month later.

It is my feeling that the demonstration that these deformities and hypokinesia and tremors and rigidity can be completely reversed for as long as a year and one-half and two years offers us a justifiably more hopeful outlook for parkinsonism. I think we will certainly understand the physiology better when we study these results and consequently we will have better medical therapy. It seems to me that since we have

demonstrated that tremor and rigidity can be completely reversed for as long as two years, we are justified in not only offering some patients surgery, but also in giving them a slightly more hopeful ultimate outlook for therapy of parkinsonism generally. I believe that surgery will come to play a larger part until medical therapy becomes more successful. These are only two of the many techniques which eventually will offer something to the patient. I feel the hazard has become less as we have gained experience. The results have become increasingly encouraging. It is an awesome responsibility to take a patient with a chronic disease and perform upon him an operation that has a considerable hazard, which might result in hemiplegia or death. Whether any individual patient is justified in taking that risk is a matter of individual decision. I wish that we could discuss some of the physiologic implications of the investigation, but time does not permit.

MODERATOR BROCK: I think we still might have a few minutes for any questions that may be submitted, because these results of Dr. Cooper's are stimulating. He has presented them with reserve and honest humility and I for one feel much impressed by these results. Perhaps we are witnesses to a landmark in the course of our approach to this subject.

Are there any questions?

QUESTIONER: *What is the oldest patient on whom Dr. Cooper has done the second procedure?*

DR. COOPER: As a matter of fact with the first procedure the oldest patient was 88, but he died. He died, apparently of a coronary thrombosis, on the third day. When we started this investigation we tried to choose the patients whom we thought had absolutely nothing to lose in trying to define its limits. I think we went too far in choosing a patient of 88 years and as helpless as he was and he died. With the second procedure we have done one in a 74 year old lady, who was able to tolerate it under local anesthesia, who has not had as good a result as the man who got up and walked away, but she is quite markedly improved. However, that was done recently. I have operated upon a man of 66, the same operation, and he stood the operation well. I am in hopes that in the aged group, if they are still well enough to walk and have no medical disease and can stand the operation under local, all of which are trying criteria, and who do not respond to medical therapy, that we might offer this procedure to those in that group.

QUESTIONER: *Is it possible to do the procedure bilaterally at an interval of a year?*

DR. COOPER: That is a problem with which we are wrestling with reference to the anterior choroidal operation. As Dr. Doshay can probably recall, we had a couple of patients who did well after one-stage. It was the beginning of my series and I was deceived because they did so well. About two months later I did the second side and two died in a row. We had most of the mortality in this entire investigation in one month, the month of August two years ago. As a result, I did few bilateral cases for a long, long time, so that our good results might live and enjoy the benefit of the result that they had and so that I might follow them and see whether the symptoms recurred and whether the operation was worth continuing. Within the last two months I have brought back two on whom I had done the choroidal occlusion on one side and chemopallidectomy on the other and both are good at the moment but I don't have the answer to that problem. I have urged some of my surgical colleagues, who have a good result with the choroidal on one side to leave them alone and follow them. It is possible that in the future chemopallidectomy which at present seems less hazardous may supplant the choroidal occlusion operation. I am not yet convinced that it will. It may, but at present we are uncertain that we can do it on one side or do the choroidal occlusion on one side or do it on both sides. I have done both sides in a woman who is 62. The result was perfect on one side and about 60 per cent improved on the other, but it is only about ten weeks since the second side was done. I have hopes that it will be possible but I don't know yet.

QUESTIONER: *Are there any effects on any of the other symptoms?*

DR. COOPER: Yes. As you could see in the film, some of them are improved remarkably in their walking, a few in speech. Speech, I think, is still one of the most difficult signs to see any improvement in. We have a couple that were speechless who can now kind of whisper. Facies has been markedly improved. Automatic movements, as you see have returned. Gait, hypokinesia and deformities have improved markedly.

SAME QUESTIONER: *Salivation?*

DR. COOPER: We have a few who have had a good result on one side but still salivate. I don't know whether the bilateral operation will remedy that or not. I have a feeling, as Dr. Brock has suggested, that

some of the salivation is due to hypothalamic involvement. I don't want to interfere with it because I don't want my lesion to extend into the hypothalamus.

QUESTIONER: *What would the incidence of good results be with the anterior choroidal?*

DR. COOPER: Two-thirds; that excludes four patients in whom I opened the head but was unable to occlude the artery for technical reasons. But of the ones occluded, two-thirds had the type of result we have demonstrated here. Out of 52, three patients had a postoperative hemiplegia and five died.

MODERATOR BROCK: *I would like to ask a question. How atypical is the anterior choroidal and how do you anticipate running into two anterior choroidals,—through arteriograms?*

DR. COOPER: The anterior choroidal operation may eventually be of more historical and physiologic interest, for the reason that you suggest. This variability of the artery frightened many people into thinking that it should not be attempted because if an artery was put there by nature, it consequently has variations. I think that is why we sometimes get hemiplegia from it. Probably when it goes into the hypothalamus we get some of the pre- or postoperative problems. It has been consistent enough for me to get good results in about two-thirds of the cases. Some of the best results have been obtained when the artery looked atypical. In the next to last patient on the film, who was seen bouncing the ball after operation,—that man's choroidal artery came off the posterior communicating. We could recognize it because we had an arteriogram. Despite this variation, the result was excellent. That is a bona fide criticism of the procedure, nevertheless. Until we get something better we have to take the risk of that variation of the vessel. But I am in hopes that having demonstrated what is possible, we can go along and develop safer and better techniques. I am not sure that we have done so yet but I have no question that we will, just as Dr. Doshay and Dr. Constable feel that we will have better medication.

MODERATOR BROCK: *Do you do an arteriogram before each?*

DR. COOPER: I do. It is indispensable. Many people do not. Despite the fact that we have urged the arteriogram as indispensable, many do the operation without it. I think you will miss the vessel occasionally without the arteriogram.

QUESTIONER: *What were the pathological changes in the patients who expired?*

DR. COOPER: We had two postmortems,—both bilateral cases. The principal lesion was in the globus. Interestingly, they showed lesions in the small ventro-lateral nucleus in the thalamus, and in the reticular substance. After the case of accidental anterior choroidal occlusion we were looking for a rationale as to why we should go on and continue the operation. We found two classical anatomical studies by Abbe on the anatomy of the choroidal artery. He pointed out that the anterior choroidal artery developed phylogenetically and embryologically in conjunction with what appeared to be a specific extra-pyramidal unit; the globus pallidus and its connections through the ansa with the reticular formation, ventrolateral thalamus, and the substantia nigra. In one patient the lesion extended into the internal capsule. On one side of the other patient it extended into the hypothalamus. I think what will be most significant in our anatomical findings as regards future therapy and future understanding of the physiology of this disease is when we eventually can examine the brains of some of the successful results. We will then be sure what the lesion is which has produced these findings. I think what we know now, as the result of these operations, as well as the result of Meyers' work, and Spiegel and Wycis' work, as well as others, is that the globus is principally involved. We are also sure it is not solely involved and we would not incriminate it entirely. Our idea of physiology is entirely reversed from what it was a few years ago when Bucy postulated that the globus was an inhibitory structure. I think one is justified in postulating that it is probably a facilitatory structure.

QUESTIONER: *How do you select the patients for the new procedure?*

DR. COOPER: I think they should be seriously ill enough to warrant brain surgery. I think they should not be at all thoroughly controlled by medical therapy and be a reasonable risk. They should preferably still be ambulatory, at least as much so as some of these reported were ambulatory with help. I think the degree of risk of death is directly proportional to the degree of vegetative symptoms that these patients show preoperatively. For the new procedure we have broadened our outlook and are willing to consider a much wider group than we were with the anterior choroidal artery occlusion. As Dr. Doshay pointed out, the choroidal operation cannot be considered in the geriatric group. We had

the best results in the idiopathic and post-encephalitic groups in this second procedure. From time to time, in suitable cases, I am going to try chemopallidectomy on arteriosclerotics. One must appreciate the fact that the aged arteriosclerotics have diffuse brain disease and a small lesion in the globus pallidus may help the tremor but may not help the diffuse brain disease at all, and consequently, one must evaluate what we are going to get as the result of even a successful operation before you decide to subject the patient to that kind of an operation under local anesthesia, which is hard on them.

QUESTIONER: *Have you done a bilateral?*

DR. COOPER: One patient with chemopallidectomy on both sides. From my observation, I have the feeling that the chemopallidectomy is not as extensive an operation as the first procedure. With the second procedure, I am not yet certain that we could duplicate the results obtained in a patient like the first one shown in the film, who was so completely deformed. I have never seen that type of result from any other type of operation in anyone's hands. I hope that we can do it with this because this is safer, but I would not want to say at the moment that we could.

QUESTIONER: *How do you explain the two fatalities following chemopallidectomy?*

DR. COOPER: One had an acute renal shutdown. The other died on the eighth postoperative day. Two hours before he became comatose we had a postoperative note that he appeared to have an excellent result. At that time he was alert and appeared well. He developed a violent coughing spell at 5:30 P.M. By eight o'clock he had become completely comatose with signs of marked increased intracranial pressure. We tapped his ventricle, and decompressed the brain with a subtemporal craniectomy. He had massive cerebral edema with herniation of the cerebellum. Death was probably secondary to an intracranial hemorrhage and cerebral edema which occurred on the eighth day. This was at least aggravated by the spell of violent coughing, resulting in early death from respiratory failure. As I said, the first one was due to renal shutdown, also unexpected. There is no danger-free operation. I doubt there ever will be. These people, particularly the ones we are operating on, are seriously sick people. They become incapacitated and sometimes paralyzed just from emotional shock and going through brain surgery under local anesthesia. Putting a lesion inside their brain

in the basal ganglia, which have heretofore been privileged territory as far as attack by neurosurgeons, carries a danger.

QUESTIONER: *Curiosity compels me to ask this question: What was the occasion on which you tied off the choroidal artery and made the brilliant observation?*

DR. COOPER: I was going to do one of the more classical, one of the earlier operations in a young man who had tremor and rigidity only on one side, a truck driver who could no longer work. In approaching the cerebral peduncle to cut it we tore the vessel. He was a post-encephalitic patient with marked adhesions, which gives me a little bit of an excuse for tearing it. At any rate we tore it. To this day I am not certain that it was the anterior choroidal artery. I am not sure how anyone could be. At any rate I thought that it was because it was in about the position where it should be. By coincidence, I had recently read an article by Leo Alexander of Boston, a classical piece of work and a brilliant paper on the blood supply of the basal ganglia, outlining the role of the anterior choroidal artery and he had even suggested that the name be changed to pallido-hippocampal artery, because of its extreme importance to these structures. We were able to stop the vessel bleeding. We decided to wait and see what happened. That was the occasion for it.

MODERATOR BROCK: I think you have had a treat and I want to thank this panel on your and my own behalf for having thrown more light on a territory which used to be a kind of dark continent. It is not now so dark and there are more lights coming on.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting, January 27, 1955, at The New York Academy of Medicine

*The Transfer in Humans of Skin Sensitivity of the Tuberculin Type with Components of Disrupted Leukocytes**

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Chase's original observation in the guinea pig[1, 2] has been extended to man with the result that it is possible to transfer regularly bacterial sensitivity of the delayed tuberculin type to non-sensitive human subjects.[3-6] This is accomplished by means of an intradermal and/or subcutaneous injection of leukocytes isolated from the blood of appropriately sensitive donors. In each of the studies cited intact viable leukocytes were used.

We have been concerned more recently with efforts to identify the component(s) of the leukocyte which may be the active material responsible for the transfer of delayed sensitivity in humans. The discussion which follows is a summary of the results of this study which has been published elsewhere in detail.[7]

In order to attempt identification of the active principle it has been necessary to get the components of the leukocytes into solution and test the capacity of such suspensions to effect the transfer of delayed sensitivity. It was observed that successful transfer of delayed skin sensitivity to partially purified preparations of the streptococcal M-substance (Type I)* could be accomplished in the negative recipients of components of leukocytes obtained from sensitive donors and disrupted by distilled water lysis. This was done using the nucleoprotein sediment in cytoplasmic solution in six consecutive instances and using the cytoplasmic supernatant solution alone in three consecutive instances.

The transfer of delayed skin sensitivity to streptococcal M-substance was also successful in four consecutive instances when components of leukocytes completely disrupted by means of repeated freezing and thawing (seven to ten cycles) were used.

It was considered desirable to substantiate these observations using tuberculin as the test material. Leukocytes obtained from tuberculin sensitive donors were disrupted by repeated freezing and thawing and the components were injected into each of three tuberculin negative recipients. Each recipient subsequently developed generalized delayed skin sensitivity to tuberculin.

The regularity of the results achieved with components of disrupted leukocytes allowed the attempts to identify the active material in such preparations to go forward. An ap-

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* Kindly supplied by Dr. R. C. Lancefield. The use of the term M-substance is not meant to imply chemical or immunologic purity.

proach to this phase of the problem has been made with the selective enzymatic treatment of disrupted leukocyte components with the specific enzymes, desoxyribonuclease (DNase) and ribonuclease (RNase) respectively.

The events following cellular transfer in humans suggest analogies to other biologic systems where the self-replication of a foreign material is fostered by the cells of the host. This is exemplified by the role of the DNA in pneumococcal transformations and the intracellular replication of viral particles and bacteriophage. The analogy is suggested by the fact that in relation to the surface area of the adult human recipient, a minute amount of donor cellular material alters the reaction capacity of the entire skin surface of the recipient in a highly specific fashion for prolonged periods. The sensitized state endures in many recipients for six to eight months and in a few for as long as one year.

The prolonged duration of the effects achieved with cellular materials suggests that the recipient may have an active role in the sensitization process presumably via an intracellular mechanism. This is in contrast to the short-lived effects of passively transferred preformed serum antibody, presumably incident to its extracellular residence in the recipient. These considerations suggest that the active material in the donor's cells may be incorporated into the cells of the recipient which are concerned with the production of delayed sensitivity. The active material in turn may alter the metabolism of such recipient cells for variable periods, in a manner similar to that by which the specific bacterium sometime in the past altered the metabolism of the cells of the donor in this regard.

In applying this working hypothesis to experimental test, two promising loci of attack appeared to be the desoxyribonucleic acid (DNA) and ribonucleic acid (RNA) components of the leukocytes. If the material active in the transfer of delayed sensitivity were assumed to be the DNA then treatment with desoxyribonuclease (DNase) might inactivate it and similarly, if assumed to be the RNA components, treatment with ribonuclease (RNase) might inactivate it. To test these assumptions 16 tuberculin negative subjects were selected and had prepared for them suspensions of components of leukocytes obtained from one of two tuberculin positive donors. Each alternate recipient received suspensions of components of leukocytes that had been frozen and thawed alone. Of the remaining eight subjects, four received suspensions of components of leukocytes which had been frozen and thawed and treated with DNase and four received suspensions of components of leukocytes frozen and thawed and treated with RNase.

In 16 consecutive instances each recipient developed generalized delayed skin sensitivity to tuberculin and the pattern of response was similar in the enzyme treated and control groups.

The specificity of the Feulgen stain and visual evidence of depolymerization of all available DNA allow one to conclude that the active material responsible for the transfer of delayed sensitivity is not the highly polymerized DNA of the donor cell components.

One cannot reach a definitive conclusion concerning the degree of depolymerization of RNA by the RNase particularly in the absence of a specific histochemical technique.

It is concluded that skin sensitivity of the delayed bacterial type can be transferred regularly with components of disrupted leukocytes. In addition, the treatment of such leukocyte components with the enzymes DNase and RNase did not diminish the capacity to transfer delayed sensitivity.

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DISCUSSION

WILLIAM S. TILLETT: Dr. Lawrence has given me the privilege of following this work with him for many years, and we have discussed it many times. I should like, in passing, to emphasize the unusual amount of labor involved in the study. It requires screening of large numbers of patients to find appropriate positive ones; it requires screening of a larger number to find negative ones, and Dr. Lawrence has been very strict with his selection of the negative patient, to see that they are really negative, and not borderline, so there is an enormous amount of tenacious quality involved in his endeavor. Dr. Lawrence has tried on occasions to transfer the reaction to animals with the cells from sensitized individuals, and I believe he has not been successful so far. Only today Dr. Lawrence told me there has been in the French literature a report that human cells could transfer this quality to animals. If this is true it will hasten the solution of a great many of these problems. If it is not true, it is equally interesting why this quality of sensitivity cannot be transferred to an animal. I won't go into that now, but it is involved in some of the conditions relating to skin transfers of a homologous and heterologous nature. Be that as it may, this has been a straightforward series of human observations that were made in the field of what in precise terms may be called allergy. I should say, in my personal opinion, that of all of the subjects that are bandied around, that treated with the greatest degree of looseness is what is clinically called allergy. The lay press have it; laymen have it; when anyone cannot eat certain foods they go to a doctor and the doctor will say "You have an allergy." He gives the patient an antihistamine, and there you are. Classically, the term allergy, which I think was first used by von Pirquet and Schick in *Serum Krankheiten*, meant altered reaction, and in my opinion it would be most helpful if the word allergy were thrown out, especially for the time being, and this situation was viewed as an altered reaction in a patient or animal who receives an initial injection of a substance which does essentially nothing; on receiving a second injection there is an altered reaction within the tissues. There are the classical experiments of specific antigen-antibody reactions which are well defined, but as the studies have developed, it now appears that it is not quite as simple as that. I think the Shwartzman phenomenon is another example. Lewis Thomas and other workers have found these extraordinary altered reactions following the second injection of a substance, and so Dr. Lawrence in this work has attempted to find the reagent in the leukocyte which is responsible for the transfer of another altered reaction. I personally was disappointed,—and nobody should be really disappointed, Mr. President, no matter how an experiment comes out,—when the DNAse did not destroy the reaction by destroying the nucleoprotein of the cell. The DNA protein carries the genes and the chromosomes, and we could picture that as being the site of the substance that is transferred. But it did not work that way. His negative results, so far, in attempting to identify the transferable substance indicate very clearly that there are a number of subtle reagents that are capable of inciting reactivity. Here a human being receives a few leukocytes locally and his whole skin surface now becomes altered to the injection of tuberculin or streptococcal materials. How small it must be, and how disseminated, and yet, although the answer may be a long way off, at least to us and to others interested in this field, it is very provocative of speculation.

Delayed Allergic Skin Responses of the Contact Dermatitis Type

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The experiments described[1-4] were aimed at elucidating some of the processes that are relevant to the elicitation of a delayed allergic skin response with simple chemicals in appropriately sensitized guinea pigs. Allergic contact dermatitis, the skin response studied, has all the essential characteristics of the delayed allergic response to tuberculin, both immunologically and histologically. Animals were sensitized with 2, 4-dinitrofluorobenzene. After a suitable incubation period they were skin tested with ten 2, 4-dinitrobenzenes which differed from each other only by virtue of the substituent on carbon one. Six compounds elicited specific inflammatory responses (elicitors) and four did not (non-elicitors). The elicitors combined chemically with proteins in the test tube and also in living animals' skin. The non-elicitors gave no evidence of so combining in either situation. The F-, Br-, and Cl-substituted elicitors (Group I) reacted *in vivo* predominantly with ϵ-NH_2 groups of lysine side chains of epidermal protein, whereas the SO_3-, SCl-, and SCN-substituted elicitors (Group II) reacted only with S of cystine or cysteine residues of epidermal protein. These results were readily duplicated when Group I elicitors were permitted to react *in vitro* with a wide variety of proteins over a broad range of pH values (7 to 11). With Group II elicitors, however, the reactions *in vivo* were duplicated *in vitro* only when hair or epidermal strips were reacted at pH 7 to 8. Quantitative studies with C^{14}-labelled dinitrochlorobenzene (DNCB) indicated that all of the dinitrophenyl groups that had combined *in vivo* with tissue constituents were so linked with amino acids that the latter may reasonably be inferred to have been residues in protein or polypeptide molecules when substitution occurred. The dinitrophenyl-protein conjugates that formed in the living skin were found by radioautography and by a histochemical technique to be localized within the epidermis. For 48 hours after applying C^{14}-labelled DNCB to the skin surface the conjugates were diffusely spread throughout the epidermis. On the third day, and thereafter, the conjugates were confined to the cornified layers of epidermis, becoming gradually more and more superficially situated. By applying DNCB to the skin at varying times during the interval between a sensitizing inoculation and the acquisition of delayed skin sensitivity (five to six days) it was possible to show that skin applications one to two days old are effective elicitors of the allergic response, whereas applications three days old, and older, were ineffective. Hence it is inferred that only those dinitrophenyl-epidermal protein conjugates which are situated in the basal, viable layers of epidermis are essential to the development of the specific inflammatory response. This zone is characteristically the site of inflammation in specific eczematous skin lesions evoked by patch tests with tuberculin and simple chemicals.

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DISCUSSION OF PAPERS BY DR. LAWRENCE AND BY DR. EISEN

MERRILL W. CHASE: Before commenting specifically on the fine work that Dr. Eisen has done, I might take a minute to review a bit of history. When the dermal sensitization of guinea pigs was first shown in Europe by Bloch and Steiner-Wourlisch[1] with Primula extract, by Mayer[2] with paraphenylenediamine, and by Frei[3] and Sulzberger[4] with neoarsphenamine, the question arose as to the area in which further progress would be made in the field of sensitization. Except in the case of paraphenylenediamine, the known sensitizers afforded no homologous chemical series for study, and even with p-phenylenediamine the limitations were such that nearly a decade passed before the cross-reactions with related compounds were studied by Nitti, Bovet and Depierre.[5] Further, the studies with neoarsphenamine could not be reproduced in this country by the original workers. Landsteiner (with whom Jacobs was associated at that time) learned from reports by Wedroff[6,7] that factory workers in Russia had become sensitive to dinitrochlorobenzene. In this, Landsteiner with his chemical training saw the potentialities of such a simple sensitizing chemical, a chloro- and nitro-substituted benzene, for such substitutents can be, as it were, "permuted" in all sorts of ways around the benzene nucleus. You have met only a few of these tonight. From this beginning with 2:4 dinitrochlorobenzene, there has burgeoned an increasing body of literature. For example, Landsteiner and Jacobs[8,9] studied some 17 compounds of the long series of nitro- and chloro-benzenes, ascertained which among them possessed the sensitizing capacity, and were then able to show that this property is present when a compound possesses a replaceable chemical radicle. From this work proceeds directly the precise chemical studies of Dr. Eisen.

The two chief problems in experimental sensitization are these: First, what happens when the sensitizing chemical is applied to the skin of a normal animal? What are the special events that go on in the animal's economy? We know that a cellular mechanism comes into being along with the event of sensitization of the animal, such that one may transfer the sensitivity from this animal to a normal individual by means of its white cells. In the second place, having provided oneself with a sensitized animal, and having applied a test dose which one knows will elicit the delayed type of reaction, what is the sequence of events that leads to the allergic response?

In both of these fields Dr. Eisen has contributed valuable and needed information. It is obvious from Dr. Eisen's demonstration that a chemical allergen which is applied to the skin at a time when the animal is not yet sensitive does not remain on or within the skin, either free or protein-bound, in appreciable amount to give more than minute "flare" reactions at the onset of sensitization; for effective contact testing, the allergen must be applied close to the onset of sensitization or after the animal has become sensitive. Dr. Eisen's conclusions in this regard are but reinforced by what we have done in our own laboratory with cellular transfer: a test dose to be effective must be applied only at the time when the cell-recipient is ready to react. In other areas, one may direct questions, perhaps usefully, at the conclusions that Dr. Eisen has reached. If Dr. Eisen sprays the shorn skin of a normal animal with a chemical allergen of the 2:4 dinitrophenyl series, using a chemical that does not of itself prove irritating to skin, hydrolysis of the sprayed skin will yield terminal amino acids affixed to the dinitrophenyl radicle, the amino acids differing according to the chemical properties of the dinitrophenyl compound used: for example, the radicle may be found attached to lysine or to cysteine. The localization of allergenic radicles in the skin is of exceeding importance for future studies; but I believe that the question remains whether the compounds found in the skin (prior to hydrolysis) represent the actual sensitizing material. Is it proper to conclude that the sensitization is actually effected in the skin sites in which preparatory injections are made in the normal animal? Or does the allergenic stimulus arrive at some more

remote site? Do you have an answer to that, Dr. Eisen?

HERMAN N. EISEN: No, not an answer, just a guess. I do not think the conjugate within the epidermis is the principal agent for the induction of sensitization.

MERRILL W. CHASE: That is one of the real problems. One can prepare conjugates consisting of the reaction product of allergenic chemical with proteins, quite analogous to what one may suppose to be formed in the skin following intradermal injection. Such conjugates by and large are entirely ineffective in inducing dermal contact-type sensitivity, excepting in the special case when one injects, concurrently, tubercle bacilli with their special waxy coating. In this particular case one effectively sensitizes the skin of the animal, even when all injections have been made into the peritoneal cavity or deep into the nuchal muscles. Hence the demonstration of conjugates as such in local areas of skin after injection of an allergen does not allow one to conclude surely if such conjugate was the actual material that induces dermal hypersensitivity in the animal: the chemical or its effective inter-action products may have diffused further into the tissues.

Another matter which makes evaluation of the experiments difficult is the high concentration of chemical used as spray on these animals, especially of the radioactive allergen. One wonders about the inflammatory alterations induced in normal skin owing to the highly irritating character of such high concentrations. For example, 1 per cent solution of 2:4 dinitrochlorobenzene in a glyceride oil or a one-quarter per cent solution in alcohol can be used on the skin without causing any gross alterations in the tissue; but when you multiply these concentrations by two-, five-, or ten-fold the irritative response of the skin will increase progressively and one will see plainly that the skin is far from normal. On and within this markedly inflamed dermal tissue the rates of penetration and diffusion may well be vastly different than in normal skin. Likewise, cellular migration may be different in kind and in degree, so that the removal of radiotracer allergen may follow an unusual rather than a normal pattern.

A point of interest which pertains to this work is the degree of parallelism between man and guinea pig with respect to the chemicals here employed: so far as information goes, when one can sensitize the guinea pig with a compound of this chloro- nitro-, substituted benzene series, it will sensitize man, and *vice versa*. There exists some uncertainty, however, regarding symmetrical trinitrobenzene. Some years ago Landsteiner and Jacobs[8, 9] concluded that it failed to sensitize guinea pigs. Sulzberger[10] subsequently reported, however, that just one individual out of a group treated with it became sensitized. Whether the preparation was impure or whether there was a mix-up in the records I cannot say.

HERMAN N. EISEN: In regard to the last question, we have never tried symmetrical trinitrobenzene, but I would be very much surprised if it were an active compound, because chemically it would be very much like dinitrobenzene, and that is inactive. The question you raised of the possibility that the inflammation produced by the very high concentrations of some of the elicitors may lead to spurious results is, of course, something we have considered. Using the active compounds of Group I, in high concentration, causes a great deal of inflammation; the epidermis is so damaged that it is removed without any difficulty. But this is true of Group I; it is not the case with the second group. Moreover, the results obtained by high concentrations of Group I compounds were duplicated when "physiologic" concentrations of a radioactively labelled Group I compound were used, i.e., C^{14}-labelled 2, 4-dinitrochlorobenzene, 0.01 M.

MERRILL W. CHASE: With regard to the second group of compounds, do you have any non-sensitizing radioactive compounds that are analogous to the radioactive allergen? If so, have you seen "granules" of the non-allergen disappear in similar fashion, and particularly in the absence of non-specific inflammation?

HERMAN N. EISEN: No, we would be very anxious to work with that compound, but we do not have it. There is no doubt that a Group II compound, like 2, 4-dinitrobenzenesulfonate does penetrate into the

animal; we have this material labelled with S^{35} but unfortunately the radioactivity here is on a labile substituent.

MARY A. MARCUS: I would like to ask Dr. Lawrence whether he determined the Rh factor in the blood of these subjects, either donors or recipients.

H. SHERWOOD LAWRENCE: No Rh determinations were done.

MERRILL W. CHASE: I should like to address a philosophical question to both Dr. Lawrence and Dr. Eisen: I wonder if they each feel that their efforts are being expended in the realm of immunology?

H. SHERWOOD LAWRENCE: That is a difficult question to answer, especially since we do not know exactly what type of material(s) we may find ultimately, but I think that the material(s) in white cells which may be concerned with the transfer of delayed sensitivity could turn out to be a system about which we have no knowledge now. The hope would be of identifying the material and quantitating it, so that with it in solution one could subject it to the conventional immunochemical techniques.

Following identification of the active material(s) one might identify the cell type from which it came and also perhaps discover which of the multiple antigens in the tubercle bacillus and in the streptococcus are instrumental in causing it to appear in the cells of the donor.

WILLIAM S. TILLETT: I would like to tell Dr. Chase that Dr. Lawrence's first article was published in The Journal of Immunology.

MERRILL W. CHASE: I should like to offer a comment on Dr. Lawrence's paper. In the slide summarizing Dr. Lawrence's findings following the onset of sensitivity, the response of individuals fitted pattern 1 or pattern 2. In the latter, however, each dot determining the position of the graph represents a fresh skin test, and there are many successive tests on the same individual. Hence with regard to the sudden rise in sensitivity that was found eight weeks after the cell transfer, one may wonder whether the finding of pattern 2 was occasioned in some way by the many successive skin injections. Of course the ordinary view would be that the tests are simply measuring the occurrence of an event that was independent of the testing procedure.

H. SHERWOOD LAWRENCE: We have been concerned with the problem of the effect of repeated skin testing on this response, and in answer to Dr. Chase's question the only basis we have for concluding that we have induced sensitivity is the fairly well documented observation that repeated skin testing with tuberculin alone does not by itself cause the appearance of delayed sensitivity to tuberculin in the negative reactor. However, we are operating at a different level than in the guinea pig where one can be certain the animal is not sensitive and has never been sensitized before. One of the possibilities is that there may be some subjects who are now skin-negative, but may have some time in the past met the specific bacterium, and in those individuals we may be recalling an old sensitivity that existed some time in the past. How to resolve this dilemma is difficult. At present the immediate problem is identification of the active material in the cell. If one could measure and quantitate it with skin sensitivity perhaps this situation might be clarified. One might be able then to distinguish between these two types of tuberculin sensitivity, the one individual who has never met the tubercle bacillus before, and the other who has met it, become positive, and subsequently negative again (as many subjects do after BCG, and some patients do after their primary complex). Without a well documented history there is no way of telling the two states apart at present.

MERRILL W. CHASE: Perhaps the individual whose response fits pattern 2 is not to be viewed simply as one who has received just multiple test doses of tuberculin, or streptococcal extract or vaccine, for he may be altered specifically because of the injection of donated cells.

H. SHERWOOD LAWRENCE: Yes, and I think the small degree of sensitization achieved early would indicate whatever the active material(s) in the leukocytes is, it exists in greater amount in the individual in pattern 1 who developed sensitivity early.

MERRILL W. CHASE: Have you ever carried out *repeated* skin tests with a non-related skin-test material in parallel with

the specific test substance, on an individual who has been converted to allergic reactivity by means of cells? In other words, has it been shown that the non-related test material fails to induce an allergic response throughout the series of tests made with it? The transfer of cells might engender a state favorable to active sensitization.

H. SHERWOOD LAWRENCE: We have not transferred sensitivity to the two materials simultaneously.

MERRILL W. CHASE: A final point concerns the slide in which you considered the similar pattern of response secured by intact and disrupted cells. Was not a greater volume of cells employed in effecting transfer with lyzed material than you would use if the cells were living?

H. SHERWOOD LAWRENCE: That is correct. As time went on our method of isolating leukocytes from the peripheral blood improved and we achieved greater yields toward the end.

HERMAN N. EISEN: I would like to have Dr. Chase answer the question he asked Dr. Lawrence and me: does he have an opinion as to whether these delayed reactions are immunological, by which I mean they are due to antigen-antibody reactions.

MERRILL W. CHASE: In a broad sense I think they are.

FRANKLIN A. STEVENS: Clinically when a site is infected or injected with dead bacterial antigen that site is more sensitive and stays sensitive longer than any other areas, and I was wondering whether this is true here, where the transfer was by disrupted cells.

H. SHERWOOD LAWRENCE: The only information we have concerning that question is that in individuals in whom cells have been injected and the cell sites have disappeared, as one repeated the skin test in the forearm, the formerly quiescent cell depots would occasionally flare up with a local reaction at the time of the tuberculin reaction in the forearm. A similar finding has been produced intentionally in animals with induced tuberculin sensitivity following cell transfer by the injection of large amounts of tuberculin parenterally.

Another related observation results when the cell site is challenged with the test material, one can induce local and later general sensitivity with a much smaller amount of cellular material. The only observation I can recall that might add further information occurred in one individual in whom we did a cellular transfer and challenged the site of leukocyte deposit with tuberculin. Initially only the cell site responded with a positive reaction—and sites similarly prepared with serum and erythrocytes—as well as unprepared sites, remained negative. When challenged with tuberculin 16 days later the old leukocyte site, a recently applied leukocyte site, and unprepared sites each gave positive reactions.

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NEW YORK PATHOLOGICAL SOCIETY

ABSTRACT OF PAPER AND DISCUSSION*

Presented at the Meeting, February 24, 1955, at The New York Academy of Medicine

The Clot-Density Method of Determination of Fibrinogen in Acute Myocardial Infarction

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The concentration of fibrinogen in the plasma has been known to rise in the presence of any inflammatory process and particularly in association with necrotization. Utilizing a technique of rapid fibrinogen determination previously developed by two of us (S.L. and B.W.V.)[1] we have found in serial studies that the concentration of this plasma protein may be considerably elevated in a variety of clinical conditions such as rheumatoid arthritis, acute rheumatic fever, decubitus ulcers, and diabetic and arteriosclerotic gangrene. These elevated fibrinogen levels tended to decline to normal whenever the clinical status improved. A significant elevation of the fibrinogen level was noted in cases of acute myocardial infarction. It was followed by a fall upon clinical improvement. In a group of 50 patients, the maximum fibrinogen elevation during the first week of illness thus corresponded with the severity of the clinical manifestations. Moreover, a correlation between the maximum fibrinogen level and the mortality rates became apparent. In the group of patients whose highest fibrinogen concentration was below 800 mg. per 100 cc. the mortality rate was 9.7 per cent. On the other hand, in the group of individuals in whom the fibrinogen level was above 800 mg. per 100 cc., the mortality rate was 42.1 per cent.

The sedimentation rate is still widely used as a laboratory guide in the evaluation of the clinical status of patients with acute coronary occlusion. Since the report of Fahræus,[2] elevation of the fibrinogen level has been known to represent the most important factor responsible for the acceleration of the sedimentation rate. It is commonly accepted that the suspension-stability of the blood depends, in addition to the fibrinogen concentration, upon the various globulins, the viscosity of the plasma, the electrostatic charge of the plasma proteins as well as that of the red blood cells, the size of the red blood cells, and the quantitative ratio of red blood cells to plasma as represented by the hematocrit reading. The multiplicity of factors influencing the sedimentation rate detracts considerably from the reliability of this test as an index of inflammatory activity. We have demonstrated, by *in vitro* studies, that the sedimentation rate may remain normal in the presence of an elevated hematocrit reading despite severe clinical manifestations associated with acute myocardial infarction. It seemed, therefore, that a test which depended solely upon the concentration of one plasma protein, such as fibrinogen, in expressing the response to an inflammatory stimulus, would be superior to the sedimentation rate. Such a procedure, which is rapid and requires only small quantities of plasma, appears to be available in the clot

* Manuscript received December 1955.

density method of determination of fibrinogen.

The technique entails the incubation of 0.1 cc. of citrated plasma with an equal amount of Difco-thromboplastin at 37° C in a microcuvette. The plasma is obtained from the admixture of one part of 0.1 molar sodium citrate to nine parts of venous blood after centrifugation for three minutes at high speed. Subsequently, the microcuvette is placed in the micro-adapter of a Coleman Spectrophotometer Junior Model 6A and 0.1 cc. of 0.02 molar calcium chloride is swiftly blown into the microcuvette. At this moment, a stopwatch is clicked. The galvanometer lightbeam comes to a standstill and the optical density is read from the upper scale. After a time interval which indicates the prothrombin time, the lightbeam begins to swing to the left, indicating the onset of coagulation. Within a few seconds, the lightbeam again comes to a standstill and the optical density is recorded anew. The difference between optical densities, before and after coagulation, has been termed "clot density." It has been shown that the fibrinogen concentration can be derived from the "clot density" by the application of the formula: $F=18d+120$, wherein F indicates the fibrinogen concentration in mg. per 100 cc. and d represents the "clot density." The normal clot density varies from 5 to 15 corresponding to a fibrinogen concentration range of 210 to 390 mg. per 100 cc.

The results of clinical studies in acute myocardial infarction strongly suggested that the fibrinogen concentration may vary in proportion to the extent of the infarcted area. While the fibrinogen concentration was very high in patients who were severely ill, patients with coronary insufficiency and transient clinical and electrocardiographic manifestations did not exhibit any rise of the fibrinogen level beyond normal values. In order to verify experimentally the assumption of a direct correlation between the extent of myocardial infarction and the fibrinogen concentration, three groups of dogs were studied.

The first group of ten animals was subjected to a sham operation in which a thoracotomy was performed with opening of the pericardial sac but without injury to the coronary arteries. In the second group of 20 animals, the descending branch of the left coronary artery was ligated just below the origin of the septal artery, thus producing a "low ligation." The third group of 20 dogs operated upon was subjected to "high ligation" of the left coronary artery, just below the origin of the circumflex ramus. The fibrinogen levels were studied in all animals prior to operation and daily for two weeks postoperatively, at the end of which time the animals were sacrificed.

All animals had normal fibrinogen levels not exceeding 340 mg. per 100 cc. before the surgical intervention. The dogs in which a sham operation was carried out responded with a rather short and transient rise of the mean fibrinogen level to 408 mg. on the second and third postoperative days, following which it declined to normal.

The animals subjected to low coronary ligation exhibited a greater rise of the mean fibrinogen level to 516 mg. per 100 cc. on the third postoperative day with subsequent normalization of the fibrinogen values.

The highest mean fibrinogen values were encountered in the animals subjected to a high ligation of the coronary artery. The peak of 588 mg. was reached on the fourth postoperative day. The fibrinogen levels in these animals remained elevated at about the same values for another two days before declining to normal.

Electrocardiographic studies before and after surgery revealed in the animals subjected to coronary ligation the presence of deep inverted T waves with coving in leads I and II as well as in the precordial leads V_3—V_6. In these leads, Q waves were also noted.

In three animals in which the procedure of a high coronary ligation was carried out the fibrinogen levels failed to rise beyond those observed in the animals with a sham operation. After sacrificing them it was observed that the suture of the coronary artery was not sufficiently tight to produce myocardial necrosis. Histologic sections failed to reveal myocardial infarction.

The results of this study seem to corroborate the initial assumption that the fibrinogen concentration reflects the extent of myocardial necrosis. Whereas all animals

subjected to a sham operation displayed a moderate and transient rise of the fibrinogen level as a non-specific manifestation of tissue breakdown caused by the surgical intervention, myocardial necrosis was associated with a more pronounced elevation. Moreover, a distinct differentiation was obtained between the animals which sustained a low ligation as compared with those which underwent a high coronary ligation. The larger area of myocardial necrosis, verified by gross and microscopic examination, was associated with a greater and more prolonged fibrinogen response.

While the correlation between area of infarction and fibrinogen level was well established in the dog, it seemed to bear out the conclusion obtained from the clinical studies that the severity of clinical manifestations paralleled the fibrinogen concentration. This, in turn, seems to suggest the possibility that the fibrinogen level may reflect the extent of the infarcted area in human myocardial infarction as well.

On the other hand, the experimental results differed from our previous clinical observations in two respects. First, the maximum mean fibrinogen concentration in dogs with high coronary ligation was 588 mg. per 100 cc., whereas the corresponding value in coronary thrombosis was 900 mg. Second, the required period of time for recovery and correspondingly for recession of the fibrinogen values to normal was about 21 days in human myocardial infarction, whereas the animals observed in this study did not display any elevations after the eighth postoperative day. This seems to be confirmed by the reversal of electrocardiographic findings at that time reported by other investigators. It therefore appears that in the dog myocardial necrosis does not stimulate the production of fibrinogen to the extent observed in man.

DISCUSSION

JOHN B. SCHWEDEL: This excellent paper merits discussion, especially in terms of the duration of the elevation of the fibrinogen level as related to the size and extent of the infarcted area. Did they correspond? In small infarctions, these levels seemed to have receded in three days, which is rather short for healing, and where more extensive infarctions occurred, in seven to eight days, which is also of short duration for large-sized infarcts. Did you correlate the pathologic with the clinical observation?

Another question: In the same hospital (yours) a few months ago a similar set of values seems to have been produced in terms of the C-reactive protein. I wonder whether these two are identical, and if they are, might that procedure be used more readily than is this?

BRUNO W. VOLK: As far as the production of myocardial infarction in the dog goes, I pointed out that the results obtained in animal experiments cannot be completely applied to the human, and vice versa. As far as the patients with acute myocardial infarction are concerned, the majority are alive. Only about five of the patients died, and there was a correlation between the size of the infarcted area and the fibrinogen levels.

As far as the last question is concerned, the work was done by Dr. Kroop and Dr. Shackman.[5] There seems to be a discrepancy between the results of our study and theirs, since the CRP becomes positive between the fifth and the ninth day, whereas the fibrinogen level becomes elevated on the second day. Moreover, according to the report of Drs. Kroop and Shackman, there was a positive CRP still present in some instances several weeks after the patient was discharged or was considered clinically cured. In our experience in uncomplicated acute myocardial infarction the fibrinogen level declines practically always during the second week.

JOHN B. SCHWEDEL: Since healing of infarcts ordinarily takes place in anywhere from as little as three weeks up to as much as nine months, and in your artificially produced infarctions the fibrinogen levels seem to have declined uniformly in three to four weeks, a discrepancy exists. We know that extensive myocardial infarcts require longer periods of time for healing.

H. P. SMITH: I would like to ask whether the fibrinogen level corresponds with the persistence of necrotic tissue.

BRUNO W. VOLK: We studied a series

of animals by killing them serially every day, in addition to those dogs in which the studies reported tonight were carried out. In a group of animals in which a high ligation was performed the fibrinogen levels remained low; however, when we sacrificed the animals, we found that the coronaries were not completely ligated and that no infarct was present. From the histologic studies we have carried out in all animals, there is a good correlation between the necrosis and the healing phase on the one hand, and the respective fibrinogen concentrations on the other hand.

JOHN S. LA DUE: How did you estimate the size of the infarcts without doing autopsies? It is difficult, if not impossible, on a clinical basis alone, to tell the size of a myocardial infarct, and there is, at best, only a rough correlation between the size of the infarction and the mortality. Whether the patient dies depends much more upon the amount of pre-existing heart disease, the development of congestive heart failure, arrhythmias and other complications.

BRUNO W. VOLK: You may remember that I was careful not to mention the size of the infarct of our patients. I am not a cardiologist, but a pathologist. The only thing I said was that these patients were clinically suggestive of massive myocardial infarction. What I meant was that the clinical picture was suggestive of myocardial infarction. I am sorry Dr. Losner is not here; he would have been able to answer this question far better than I.

SILIK H. POLAYES: I assume the patients studied did not receive any anticoagulant therapy; if so, how did you manage to keep the clinicians from giving it to them?

BRUNO W. VOLK: Some of the patients were kept on anticoagulant therapy. Anticoagulants do not affect the fibrinogen level in our experience. We have been asked that question repeatedly. Some of these patients were in an institution where the clinicians prefer not to administer anticoagulant therapy.

H. P. SMITH: You took the sedimentation rates in those patients?

BRUNO W. VOLK: Yes.

H. P. SMITH: What was the result?

BRUNO W. VOLK: The values were erratic and frequently did not correspond with the clinical picture.

SILIK H. POLAYES: What is the answer to the second part of my question?

BRUNO W. VOLK: Again not being a clinician, I can only say that there is considerable difference of opinion whether to give anticoagulant therapy or not; there are some cardiologists who are definitely opposed to giving anticoagulant therapy in patients with acute myocardial infarction except in selected cases.

H.P. SMITH: You say they believe in giving it in selected cases. I don't know just what that means.

BRUNO W. VOLK: Unfortunately Dr. Losner is not here to help me with the clinical questions, but according to some of the papers I have read, it is only those patients who are considered to be in very serious condition to whom anticoagulant therapy is administered. Only those cases are selected which are supposedly in the category of massive myocardial infarction.

H. P. SMITH: At any rate, your cases were not selected, since you have members in both groups.

ALFRED SCHWARZ: At what level of anticoagulant therapy were the patients kept?

BRUNO W. VOLK: At 10 to 15 per cent.

SHEPARD SHAPIRO: Did complications such as pulmonary infarction influence the fibrinogen level?

BRUNO W. VOLK: We have several patients with pulmonary infarction, and we have also seen patients who developed pneumonia during hospitalization. We observed a transient rise in the fibrinogen level in such complications.

MARY A. MARCUS: Did the fibrinogen level go up in the presence of complications?

BRUNO W. VOLK: In some instances, yes, depending on what complications occurred.

QUESTION: Did congestive heart failure affect the fibrinogen level?

BRUNO W. VOLK: We had a number of patients who developed congestive heart failure. In those instances the fibrinogen

stayed at slightly elevated levels, without returning to normal.

H. P. SMITH: Did the fibrinogen level run more or less parallel with the sedimentation rate in other diseases?

BRUNO W. VOLK: We have done extensive studies on a large number of diseases including rheumatic fever, and we think that the sedimentation rate is an outdated tool for the clinician because it is erratic and gives bizarre results. About a year ago a paper appeared in the *Journal of Pediatrics*[4] according to which an accelerated sedimentation rate occurs in about 15 per cent of apparently healthy children. Some of these children had a sedimentation rate of 30 or even more.

H. P. SMITH: You would be willing to use fibrinogen levels in other diseases in preference to sedimentation rates?

BRUNO W. VOLK: Yes.

ABRAHAM SCHWEID: How do the fibrinogen levels vary in rheumatic carditis?

BRUNO W. VOLK: We have studied the fibrinogen levels serially in a number of patients with acute rheumatic carditis. There is always an initial significant rise, followed by a decline when the clinical condition improves. We have observed also in this type of patient that the fibrinogen concentration is higher in those individuals who appear to be more seriously ill.

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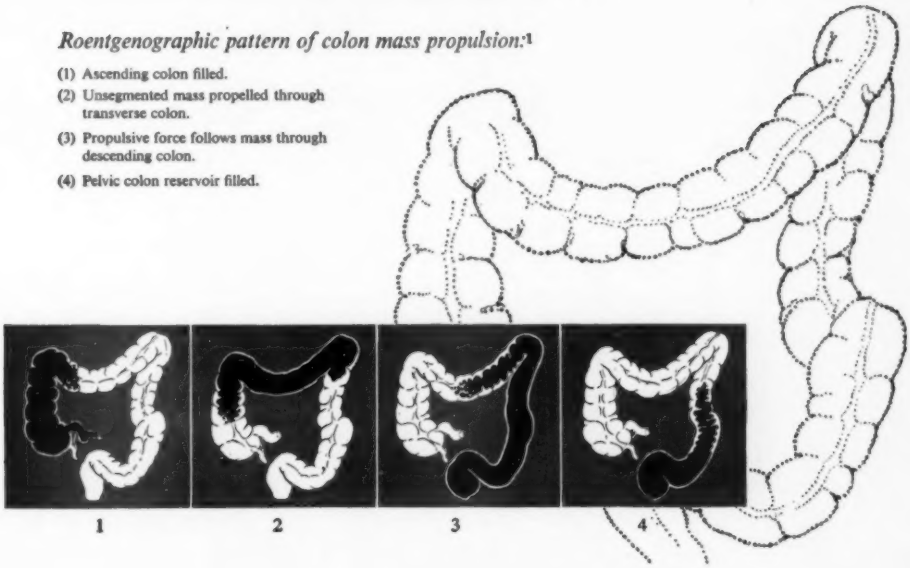
SMOOTHAGE ACTION IN CONSTIPATION

Roentgenographic pattern of colon mass propulsion:[1]

(1) Ascending colon filled.
(2) Unsegmented mass propelled through transverse colon.
(3) Propulsive force follows mass through descending colon.
(4) Pelvic colon reservoir filled.



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Correction of constipation logically, therefore, lies in the suitable adjustment of such factors as nervous fatigue and tension, improper intake of fluid, improper dietary habits, failure to respond to the call to stool, lack of physical exercise and abuse of the intestinal tract through excessive use of laxatives.[2]

The characteristics of Metamucil permit the correction of most of these factors: it provides bulk; it demands adequate intake of fluids (one glass with Metamucil powder, one glass after each dose); it increases the physiologic demand to evacuate; and it does not establish a laxative "habit." Metamucil, in addition, is inert, and also nonirritating and nonallergenic.

The average adult dose is one rounded teaspoonful of Metamucil powder in a glass of cool water, milk or fruit juice, followed by an additional glass of fluid if indicated.

Metamucil is the highly refined mucilloid of Plantago ovata (50%), a seed of the psyllium group, combined with dextrose (50%) as a dispersing agent. It is supplied in containers of one pound – also four ounces and eight ounces. G. D. Searle & Co., Research in the Service of Medicine.

---

1. Best, C. H., and Taylor, N.B.: The Physiological Basis of Medical Practice: A Text in Applied Physiology, ed. 5, Baltimore, The Williams & Wilkins Company, 1950, pp. 579-583.

2. Bargen, J. A.: A Method of Improving Function of the Bowel, Gastroenterology *13*:275 (Oct.) 1949.

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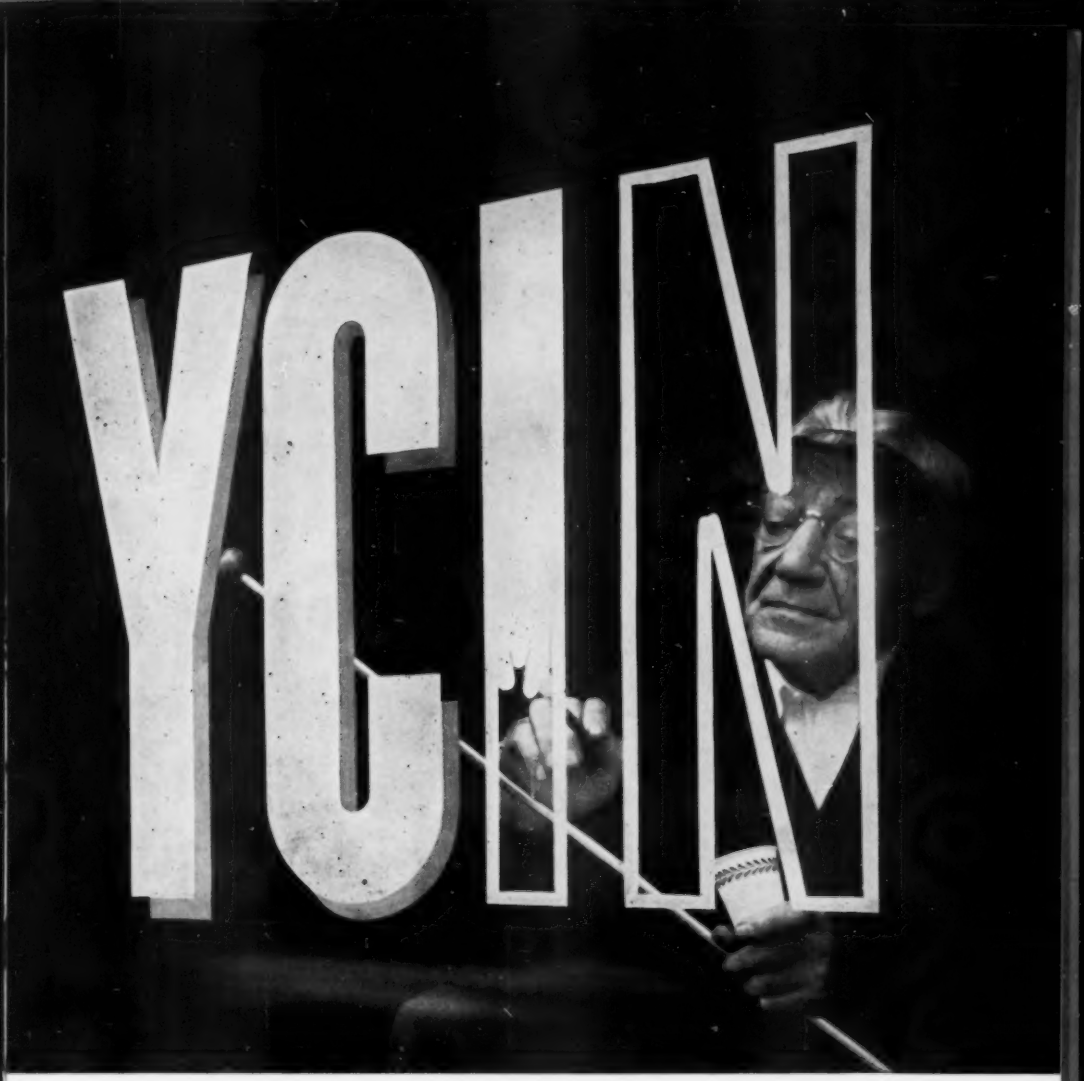

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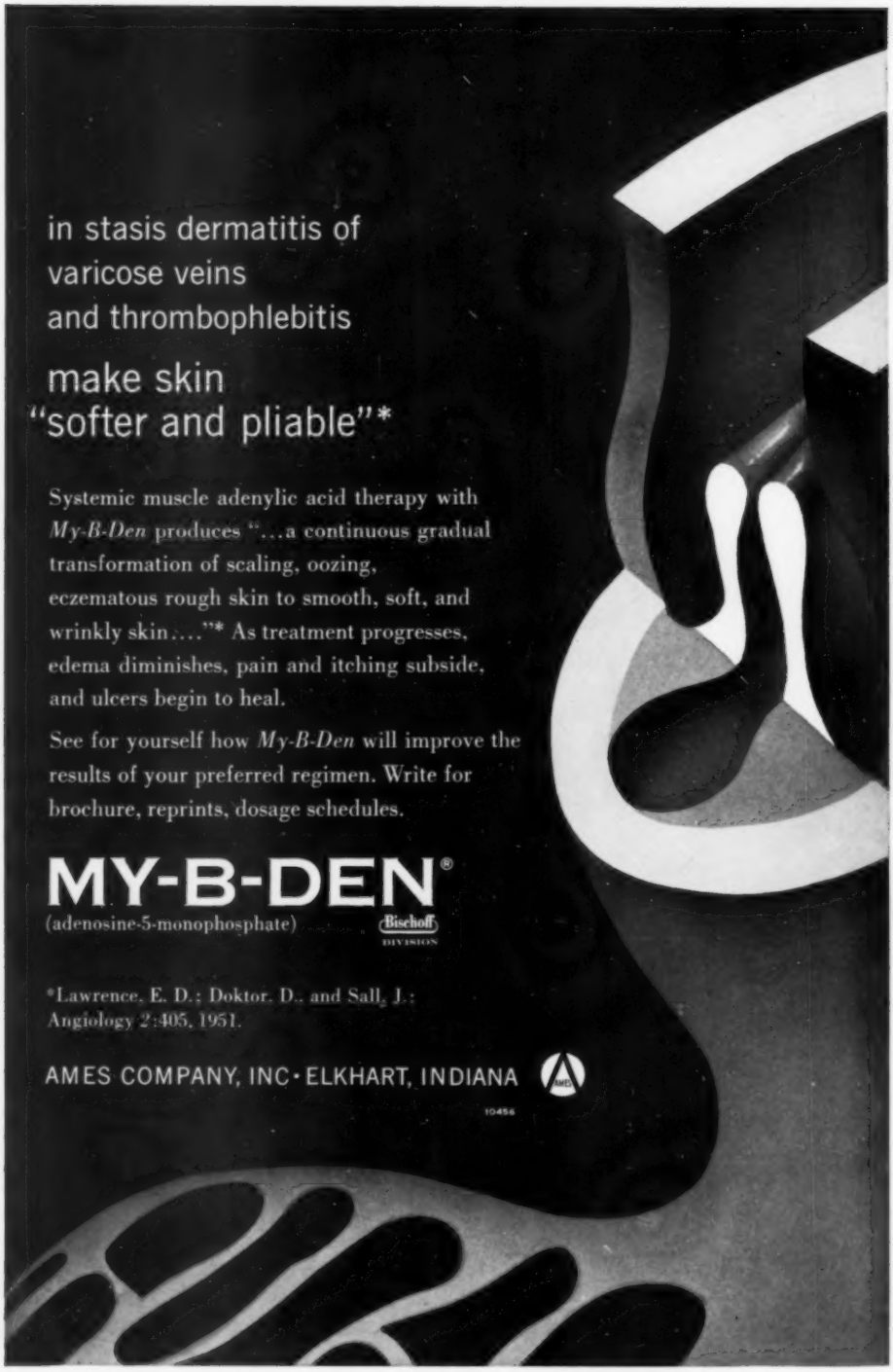
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*Lawrence, E. D.; Doktor, D., and Sall, J.: Angiology 2:405, 1951.
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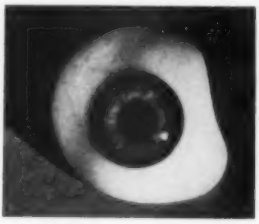

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[illegible] Clin. Med. 1: 8-9 (Sept.) 1949; 2. Chamberlain, G. J.: Missouri Med. 46: 1014, 1949; 3. Gerow, L.: Canadian Med. Ass. J. 60: 612, 1949.

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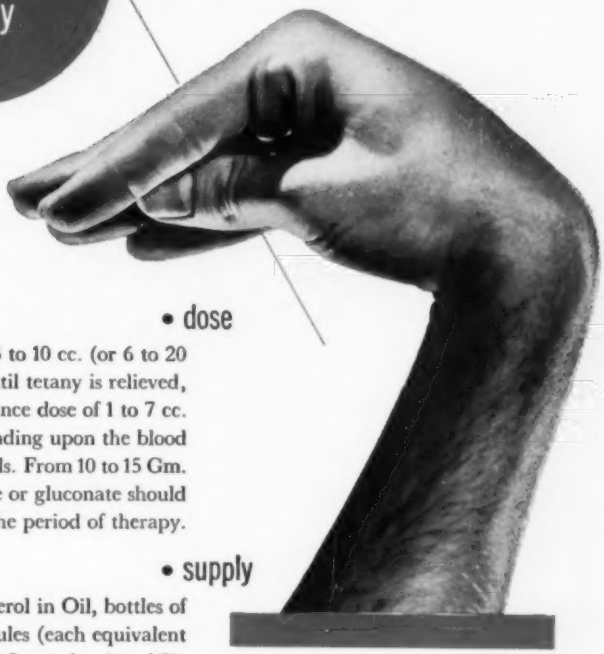

• dose

Orally 3 to 10 cc. (or 6 to 20 capsules) daily until tetany is relieved, weekly maintenance dose of 1 to 7 cc. or 2 to 14 capsules depending upon the blood and urine calcium levels. From 10 to 15 Gm. calcium lactate or gluconate should be given daily through the period of therapy.

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Violent and dread ache
That should have fame and Latin name
And yet is called "a headache."

The victim thinks his head's in kinks,
Or, from the inner clamor,
Some hidden sprite with all his might
Is banging with a hammer.

He seems to feel that rods of steel
Are thrusting through his cranium.
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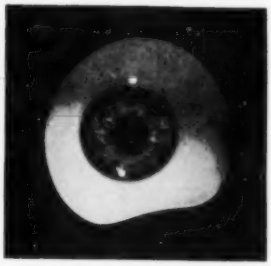

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1. J.A.M.A. 159:645 (Oct. 15) 1955.
2. J.A.M.A. 158:386 (June 4) 1955.

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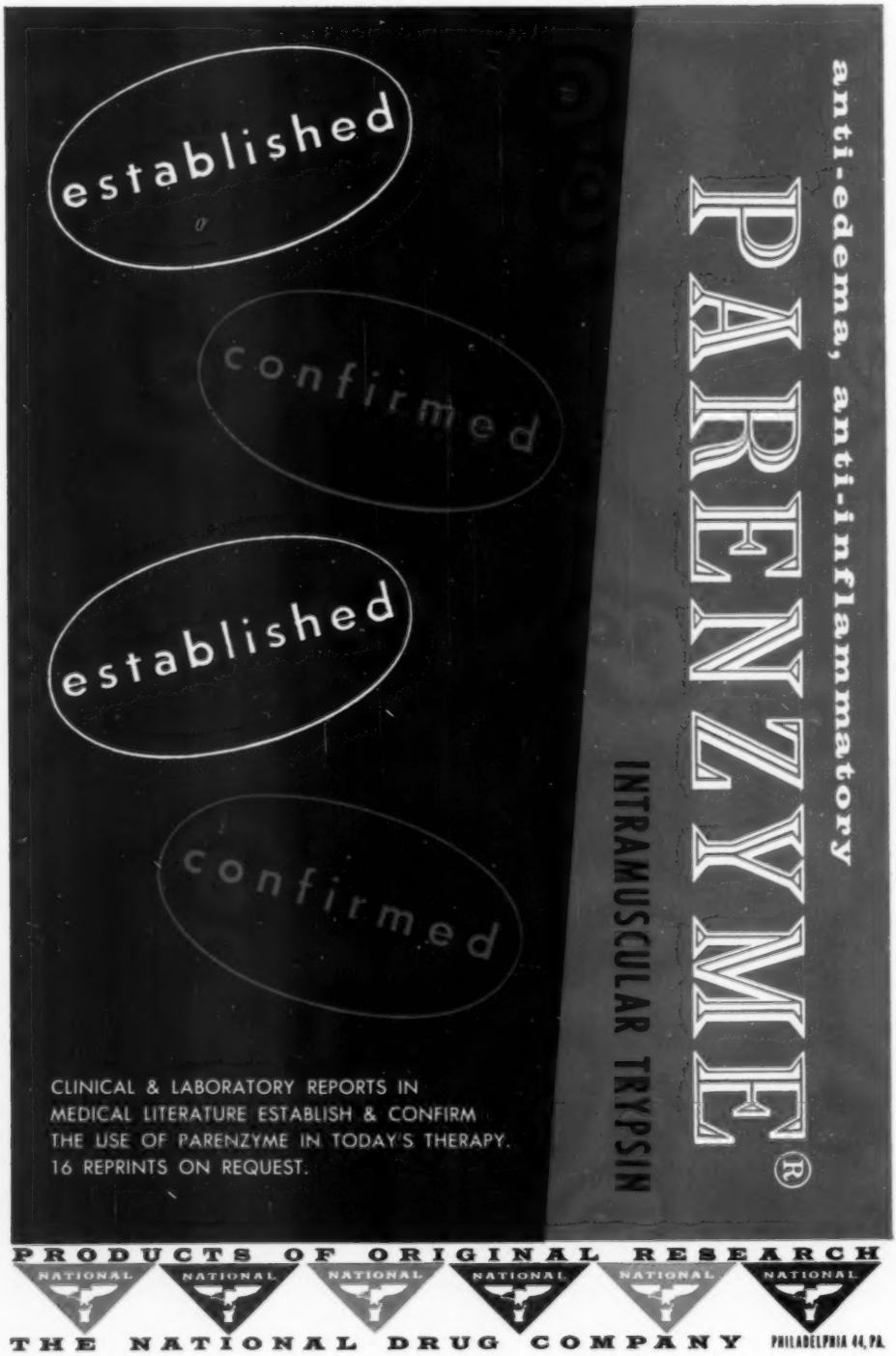
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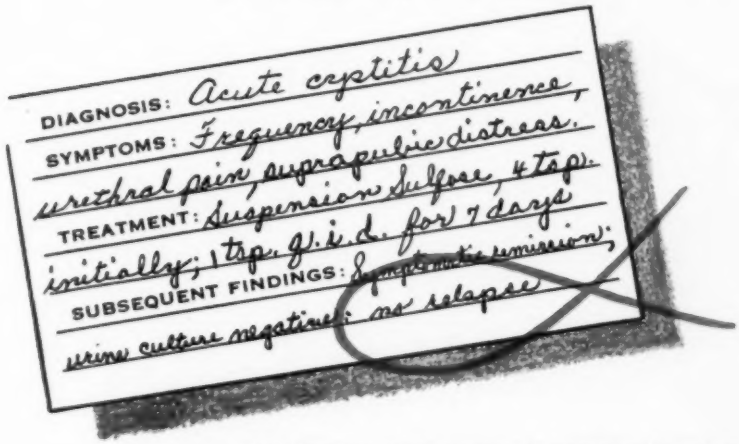
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1. Bohne, A.W., and Chase, W.E.: Am. J. M. Sc. March, 1956. 2. Berkowitz, D.: Antibiot. & Chemo. *3*:618 (June) 1953. 3. Editorial: J.A.M.A. *159*:1459 (Dec. 10) 1955.

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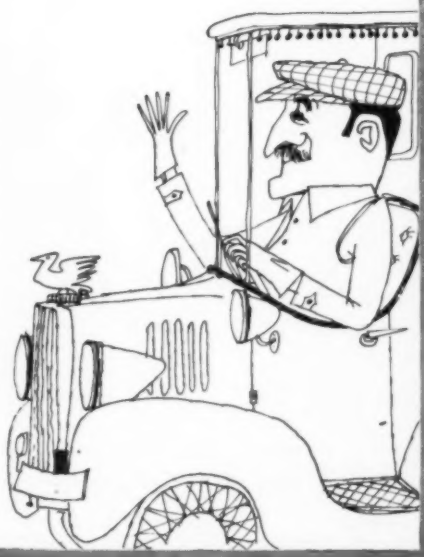

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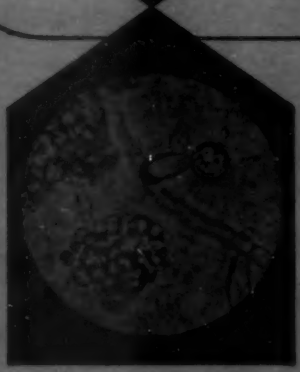

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